(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 March 2002 (28.03.2002)

PCT

(10) International Publication Number
WO 02/24684 A1

(51) International Patent Classification[7]: C07D 401/06, 401/12, 401/14, 471/04, A61K 31/47

(21) International Application Number: PCT/EP01/10976

(22) International Filing Date:
19 September 2001 (19.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0023211.6 21 September 2000 (21.09.2000) GB
0101628.6 22 January 2001 (22.01.2001) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/24684 A1

(54) Title: QUINOLINE DERIVATIVES AS ANTIBACTERIALS

(57) Abstract: Aminopiperidine derivatives and pharmaceutically acceptable derivatives thereof useful in methods of treatment of bacterial infections in mammals, particularly in man.

QUINOLINE DERIVATIVES AS ANTIBACTERIALS

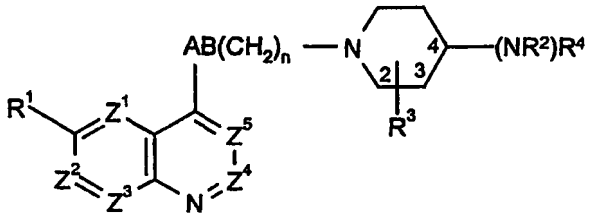
This invention relates to novel compounds, compositions containing them and their use as antibacterials.

WO99/37635, WO00/21948, WO00/21952, WO00/43383, WO0078748, WO01/07432, WO01/07433 disclose piperidine and piperazine derivatives having antibacterial activity.

WO9802434, WO9802438, WO9703069 and WO9639145 disclose certain bicyclic heteroaromatic compounds having protein tyrosine kinase inhibitor, cell proliferation inhibitor and human epidermal growth factor receptor type 2 inhibitor activity.

We have now found a novel group of aminopiperidines which have antibacterial activity.

This invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, one is CR^{1a} and the remainder are CH , or one or two of Z^1, Z^2, Z^3, Z^4 and Z^5 are independently CR^{1a} and the remainder are CH;

R^1 and R^{1a} are independently hydrogen; hydroxy; (C_{1-6})alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; trifluoromethoxy; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

provided that when Z^1, Z^2, Z^3, Z^4 and Z^5 are CR^{1a} or CH, then R^1 is not hydrogen;

R^2 is hydrogen, or (C_{1-4})alkyl or (C_{2-4})alkenyl optionally substituted with 1 to 3 groups selected from:
amino optionally substituted by one or two (C_{1-4})alkyl groups; carboxy; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, aminocarbonyl(C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-4})alkenylsulphonyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl or (C_{2-4})alkenylcarbonyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; 5-oxo-1,2,4-oxadiazol-3-yl; halogen; (C_{1-4})alkylthio; trifluoromethyl; hydroxy optionally substituted by (C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl; oxo; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or (C_{1-4})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

R^3 is hydrogen; or
R^3 is in the 2-, 3- or 4-position and is:
carboxy; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; or 5-oxo-1,2,4-oxadiazol-3-yl; or
(C_{1-4})alkyl or ethenyl optionally substituted with any of the substituents listed above for R^3 and/or 0 to 2 groups R^{12} independently selected from:

halogen; (C_{1-6})alkylthio; trifluoromethyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or

(C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or when R^3 is in the 3-position, hydroxy optionally substituted as described above;
in addition when R^3 is disubstituted with a hydroxy or amino containing substituent and carboxy containing substituent these may together form a cyclic ester or amide linkage, respectively;

R^4 is a group $-X^1-X^2-X^3-X^4$ in which:

X^1 is CH_2, CO or SO_2;

X^2 is $CR^{14}R^{15}$;

X^3 is NR^{13}, O, S, SO_2 or $CR^{14}R^{15}$; wherein:

each of R^{14} and R^{15} is independently selected from: hydrogen; halo; (C_{1-4})alkoxy; (C_{1-4})alkylthio; trifluoromethyl; cyano; carboxy; nitro; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally mono- or di-substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl, provided that R^{14} and R^{15} on the same carbon atom are not both selected from optionally substituted hydroxy and optionally substituted amino; or

R^{14} and R^{15} together represent oxo;

R^{13} is hydrogen; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

two R^{14} groups or an R^{13} and an R^{14} group on adjacent atoms together represent a bond and the remaining R^{13}, R^{14} and R^{15} groups are as above defined;

two R^{14} groups and two R^{15} groups on adjacent atoms together represent bonds such that X^2 and X^3 is triple bonded;

two R^{14} groups or an R^{13} and an R^{14} group in X^2 and X^3 together with the atoms to which they are attached form a 5 or 6 membered carbocyclic or heterocyclic ring and the remaining R^{15a} groups are as above defined;

X^4 is phenyl or C or N linked monocyclic aromatic 5- or 6-membered heterocycle containing up to four heteroatoms selected from O, S and N and optionally C-substituted by up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy; and
optionally N substituted by trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

n is 0 or 1;

A is NR^{11}, O or CR^6R^7 and B is NR^{11}, O, SO_2 or CR^8R^9 and wherein:
each of R^6, R^7, R^8 and R^9 is independently selected from: hydrogen; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;
or when n=1 R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;
or R^6 and R^7 or R^8 and R^9 together represent oxo;

provided that:
when A is NR^{11}, B is not NR^{11} or O;
when A is CO, B is not CO, O or SO_2;
when n is 0 and A is NR^{11}, CR^8R^9 can only be CO;
when A is CR^6R^7 and B is SO_2, n is 0;
when n is 0, B is not NR^{11} or O or R^8 and R^9 are not optionally substituted hydroxy or amino;
when A is O, B is not NR^{11}, O, SO_2 or CO and n=1; and
when A-B is $CR^7=CR^9$, n is 1

R^{10} is selected from (C_{1-4})alkyl; (C_{2-4})alkenyl and aryl any of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; (C_{1-6})alkylsulphonyl; trifluoromethylsulphonyl; (C_{2-6})alkenylsulphonyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; and (C_{2-6})alkenylcarbonyl; and

R^{11} is hydrogen; trifluoromethyl, (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage.

This invention also provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

In one aspect, R^4 is not phenylpropyl or phenylpropenyl in which the phenyl group is optionally substituted by up to five groups R^a wherein R^a is halogen, mercapto, (C_{1-4})alkyl, phenyl, (C_{1-4})alkoxy, hydroxy(C_{1-4})alkyl, mercapto (C_{1-4})alkyl, halo(C_{1-4})alkyl, hydroxy, optionally substituted amino, nitro, carboxy, (C_{1-4})alkylcarbonyloxy, (C_{1-4})alkoxycarbonyl, formyl, or (C_{1-4})alkylcarbonyl. In a further aspect R^4 is not optionally substituted phenylpropyl or phenylpropenyl.

In another aspect, when X^1 is CH_2, X^4 is phenyl optionally substituted by up to five groups R^a and X^2 and X^3 are each $CR^{14}R^{15}$ one of R^{14} and R^{15} cannot be hydroxy when the remainder are hydrogen. In a further aspect when X^1 is CH_2, X^4 is optionally substituted phenyl and X^2 and X^3 are each $CR^{14}R^{15}$ one of $R^{14}$and R^{15} cannot be hydroxy when the remainder are hydrogen.

In another aspect, when X^1 is CH_2, X^4 is phenyl optionally substituted by up to five groups R^a, $-X^1-X^2-X^3-$ is not $-(CH_3)_2O-$, or $-(CH_3)_2CO-$. In a further aspect when X^1 is CH_2, X^4 is optionally substituted phenyl, $-X^1-X^2-X^3-$ is not $-(CH_3)_2O-$, or $-(CH_3)_2CO-$.

In another aspect, R^4 is not a heteroaryl (C_{1-3})alkyl or heteroaroyl (C_{1-2})alkyl group in which the heteroaryl ring is optionally substituted by up to three groups R^b selected from optionally substituted amino, halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C_{1-4})alkoxycarbonyl, (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl, aryl, and oxo groups. In a further aspect, R^4 is not an optionally substituted heteroaryl (C_{1-3})alkyl or heteroaroyl(C_{1-2}) alkyl group.

In one further aspect:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, one is CR^{1a} and the remainder are CH , or one of Z^1, Z^2, Z^3, Z^4 and Z^5 is CR^{1a} and the remainder are CH;

X^3 is other than S;

each of R^{14} and R^{15} is independently selected from: hydrogen; (C_{1-4})alkoxy; (C_{1-4})alkylthio; trifluoromethyl; cyano; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally mono- or di-substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; or R^{14} and R^{15} together represent oxo;

R^{13} is hydrogen; trifluoromethyl, (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

two R^{14} groups or an R^{13} and an R^{14} group on adjacent atoms together represent a bond and the remaining R^{13}, R^{14} and R^{15} groups are as above defined;

In another further aspect:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, one is CR^{1a} and the remainder are CH , or one of Z^1, Z^2, Z^3, Z^4 and Z^5 is CR^{1a} and the remainder are CH;

R^1 and R^{1a} are other than trifluoromethoxy;

X^1 is CH_2;

X^3 is other than S;

each of R^{14} and R^{15} is independently selected from: hydrogen; (C_{1-4})alkoxy; (C_{1-4})alkylthio; trifluoromethyl; cyano; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; or R^{14} and R^{15} together represent oxo;

R^{13} is hydrogen; trifluoromethyl, (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

two R^{14} groups or an R^{13} and an R^{14} group on adjacent atoms together represent a bond and the remaining R^{13}, R^{14} and R^{15} groups are as above defined;

A is NR^{11} or CR^6R^7 and B is NR^{11}, O, SO_2 or CR^8R^9 and wherein:

each of R^6, R^7, R^8 and R^9 is independently selected from: hydrogen; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;

or R^6 and R^7 or R^8 and R^9 together represent oxo;

provided that:
when A is NR^{11}, B is not NR^{11}, O or SO_2;
when A is CO, B is not CO, O or SO_2;
when n is 0 and A is NR^{11}, CR^8R^9 can only be CO;
when A is CR^6R^7 and B is SO_2, n is 0;
when n is 0, B is not NR^{11} or O or R^8 and R^9 are both hydrogen; and
when A-B is $CR^7=CR^9$, n is 1;
and when one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they do not together form a cyclic ester or amide linkage.

Preferably Z^5 is CH or N, Z^3 is CH or CF and Z^1, Z^2 and Z^4 are each CH, or Z^1 is N, Z^3 is CH or CF and Z^2, Z^4 and Z^5 are each CH.

When R^1 or R^{1a} is substituted alkoxy it is preferably (C_{2-6})alkoxy substitituted by optionally N-substituted amino, guanidino or amidino, or (C_{1-6})alkoxy substituted by piperidyl. Suitable examples of R^1 and R^{1a} alkoxy include methoxy, trifluoromethoxy, n-propyloxy, iso-butyloxy, aminoethyloxy, aminopropyloxy, aminobutyloxy, aminopentyloxy, guanidinopropyloxy, piperidin-4-ylmethyloxy, phthalimido pentyloxy or 2-aminocarbonylprop-2-oxy.

Preferably R^1 and R^{1a} are independently methoxy, amino(C_{3-5})alkyloxy, guanidino(C_{3-5})alkyloxy, piperidyl(C_{3-5})alkyloxy, nitro or fluoro; R^1 is more preferably methoxy, amino(C_{3-5})alkyloxy or guanidino(C_{3-5})alkyloxy. R^{1a} is more preferably H or F. Most preferably R^1 is methoxy and R^{1a} is H or when Z^3 is CR^{1a} it may be C-F.

When Z^5 is CR^{1a}, R^{1a} is preferably hydrogen, cyano, hydroxymethyl or carboxy, most preferably hydrogen.

Preferably n is 0.

R^2 is preferably hydrogen; (C_{1-4})alkyl substituted with carboxy, optionally substituted hydroxy, optionally substituted aminocarbonyl, optionally substituted amino or (C_{1-4})alkoxycarbonyl; or (C_{2-4})alkenyl substituted with (C_{1-4})alkoxycarbonyl or carboxy. More preferred groups for R^2 are hydrogen, carboxymethyl, hydroxyethyl, aminocarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylallyl and carboxyallyl, most preferably hydrogen.

Preferred examples of R^3 include hydrogen; optionally substituted hydroxy; (C_{1-4}) alkyl; ethenyl; optionally substituted 1-hydroxy-(C_{1-4}) alkyl; optionally substituted aminocarbonyl; carboxy(C_{1-4})alkyl; optionally substituted aminocarbonyl(C_{1-4})alkyl; cyano(C_{1-4})alkyl; optionally substituted 2-oxo-oxazolidinyl and optionally substituted 2-oxo-oxazolidinyl$(C_{1-4}$alkyl). More preferred R^3 groups are hydrogen; $CONH_2$; 1-

hydroxyalkyl e.g. CH_2OH, $CH(OH)CH_2CN$; CH_2CO_2H; CH_2CONH_2; -$CONHCH_2CONH_2$; 1,2-dihydroxyalkyl e.g. $CH(OH)CH_2OH$; CH_2CN; 2-oxo-oxazolidin-5-yl and 2-oxo-oxazolidin-5-yl(C_{1-4}alkyl). Most preferably R^3 is hydrogen.

R^3 is preferably in the 3- or 4-position.

When R^3 and R^6, R^7, R^8 or R^9 together form a cyclic ester or amide linkage, it is preferred that the resulting ring is 5-7 membered.

When A is CH(OH) the R-stereochemistry is preferred.

Preferably A is NH, NCH_3, CH_2, CHOH, $CH(NH_2)$, C(Me)(OH) or CH(Me).

Preferably B is CH_2 or CO.

Preferably A-B is CHOH-CH_2, NR^{11}-CH_2 or NR^{11}-CO.

Particularly preferred are those compounds where n=0, A is NH and B is CO, or A is CHOH and B is CH_2, when more preferably A is the *R*-isomer of CHOH.

Preferably R^{11} is hydrogen or (C_{1-4})alkyl e.g. methyl, more preferably hydrogen.

R^{13}, R^{14} and R^{15} are preferably H or (C_{1-4})alkyl such as methyl, more preferably hydrogen.

X^1 is preferably CH_2.

X^2 is preferably CH_2 or together with X^3 forms a CH=CH group.

X3 is preferably CH_2, O or NH, or together with X2 forms a CH=CH group.

Preferred linker groups $-X^1-X^2-X^3-$ include $-(CH_2)_2-O-$, $-CH_2-CH=CH-$, $-(CH_2)_3-$, $-(CH_2)_2-NH-$ or $-CH_2CONH-$.

Monocyclic aromatic heterocyclic groups for X^4 include pyridyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, thienyl, isoimidazolyl, thiazolyl, furanyl and imidazolyl, 2H-pyridazone, 1H-pyrid-2-one. Preferred aromatic heterocyclic groups include pyrid-2-yl, pyrid-3-yl, thiazole-2-yl, pyrimidin-2-yl, pyrimidin-5-yl and fur-2-yl.

Preferred substituents on heterocyclic X^4 include halo especially fluoro, trifluoromethyl and nitro.

Preferred substituents on phenyl X^4 include halo, especially fluoro, nitro, cyano, trifluoromethyl, methyl, methoxycarbonyl and methylcarbonylamino.

Preferably X^4 is 2-pyridyl, 3-fluorophenyl, 3,5-difluorophenyl or thiazol-2-yl.

When used herein, the term "alkyl" includes groups having straight and branched chains, for instance, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl and hexyl. The term 'alkenyl' should be interpreted accordingly.

Halo or halogen includes fluoro, chloro, bromo and iodo.

Haloalkyl moieties include 1-3 halogen atoms.

Unless otherwise defined, the term "heterocyclic" as used herein includes optionally substituted aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and

sulphur, which rings may be unsubstituted or C-substituted by, for example, up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; optionally substituted aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy and oxo groups.

Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl.

When used herein the term "aryl", includes optionally substituted phenyl and naphthyl.

Aryl groups may be optionally substituted with up to five, preferably up to three, groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano, carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; phenyl, phenyl(C_{1-4})alkyl or phenyl(C_{1-4})alkoxy

The term "acyl" includes formyl and (C_{1-6})alkylcarbonyl group.

Preferred compounds of formula (I) include:

2-{1-[(R)-2-Hydroxy-2-(6-methoxy-[1,5]-naphthyridine-4-yl)-ethyl]-piperidin-4-ylamino}-N-phenyl-acetamide;
4-{*trans*-1-[3,5-Difluorophenyl]-3-propenyl}amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine;
(R)-1-(6-Methoxy-[1,5]naphthyridin-4-yl)-2-{4-[2-(pyridin-2-yloxy)-ethylamino]-piperidin-1-yl}-ethanol;
(R)-1-(6-Methoxy-[1,5]naphthyridin-4-yl)-2-[4-((E)-3-pyridin-2-yl-allylamino)-piperidin-1-yl]-ethanol;
4-[2-(3,5-Difluorophenylamino)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine;
4-[2-(3-Fluorophenylamino)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine; and
4-[*trans*-1-(2-thiazolyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxy-[1,5]-naphthyridin-4-yl)]ethylpiperidine
and pharmaceutically acceptable derivatives thereof.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

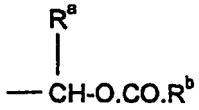
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

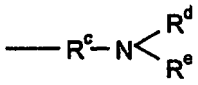
Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, p-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide. Compounds of

formula (I) having a free carboxy group may also be prepared as an *in vivo* hydrolysable ester. The invention extends to all such derivatives.

Examples of suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming groups include those forming esters which break down readily in the human body to leave the parent acid or its salt. Suitable groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):



(i)



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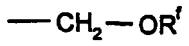

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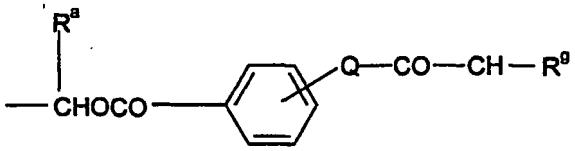
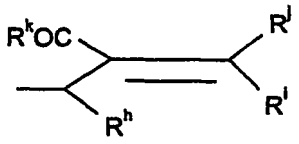


(iv)

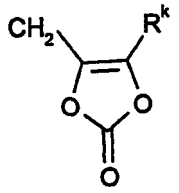


(v)

wherein R^a is hydrogen, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, methyl, or phenyl, R^b is (C_{1-6}) alkyl, (C_{1-6}) alkoxy, phenyl, benzyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyloxy, (C_{1-6}) alkyl (C_{3-7}) cycloalkyl, 1-amino (C_{1-6}) alkyl, or 1-(C_{1-6} alkyl)amino (C_{1-6}) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents (C_{1-6}) alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C_{1-6}) alkyl; R^f represents (C_{1-6}) alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C_{1-6}) alkyl, or (C_{1-6}) alkoxy; Q is oxygen or NH; R^h is hydrogen or (C_{1-6}) alkyl; R^i is hydrogen, (C_{1-6}) alkyl optionally substituted by halogen, (C_{2-6}) alkenyl, (C_{1-6}) alkoxycarbonyl, aryl or heteroaryl; or R^h and R^i together form (C_{1-6}) alkylene; R^j represents hydrogen, (C_{1-6}) alkyl or (C_{1-6}) alkoxycarbonyl; and R^k represents (C_{1-8}) alkyl, (C_{1-8}) alkoxy, (C_{1-6}) alkoxy(C_{1-6})alkoxy or aryl.

Examples of suitable *in vivo* hydrolysable ester groups include, for example, acyloxy(C_{1-6})alkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; (C_{1-6})alkoxycarbonyloxy(C_{1-6})alkyl groups, such as ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; di(C_{1-6})alkylamino(C_{1-6})alkyl especially di(C_{1-4})alkylamino(C_{1-4})alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-((C_{1-6})alkoxycarbonyl)-2-(C_{2-6})alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl.

A further suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming group is that of the formula:



wherein R^k is hydrogen, C_{1-6} alkyl or phenyl.

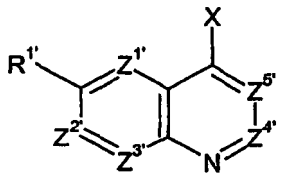
R is preferably hydrogen.

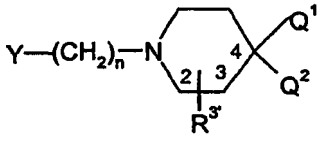
Compounds of formula (I) may also be prepared as the corresponding N-oxides.

Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. For example the invention includes compound in which an A-B group CH(OH)-CH_2 is in either isomeric configuration, the *R*-isomer is preferred. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

In a further aspect of the invention there is provided a process for preparing compounds of formula (I), and pharmaceutically acceptable derivatives thereof, which process comprises:

reacting a compound of formula (IV) with a compound of formula (V):



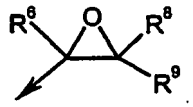


(IV) (V)

wherein n is as defined in formula (I); $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$ and $R^{3'}$ are Z^1, Z^2, Z^3, Z^4, Z^5, R^1 and R^3 as defined in formula (I) or groups convertible thereto;
Q^1 is NR^2R^4 or a group convertible thereto wherein $R^{2'}$ and $R^{4'}$ are R^2 and R^4 as defined in formula (I) or groups convertible thereto and Q^2 is H or $R^{3'}$ or Q^1 and Q^2 together form an optionally protected oxo group;
and X and Y may be the following combinations:

(i) X is A'-COW, Y is H and n is 0;
(ii) X is $CR^6=CR^8R^9$, Y is H and n is 0;
(iii) X is oxirane, Y is H and n is 0;
(iv) X is N=C=O and Y is H and n is 0;
(v) one of X and Y is CO_2R^y and the other is $CH_2CO_2R^x$;
(vi) X is CHR^6R^7 and Y is $C(=O)R^8$;
(vii) X is $CR^7=PR^z{}_3$ and Y is $C(=O)R^9$ and n=1;
(viii) X is $C(=O)R^7$ and Y is $CR^9=PR^z{}_3$ and n=1;
(ix) Y is COW and X is $NHR^{11'}$ or NCO or $NR^{11'}COW$ and n=0 or 1 or when n=1 X is COW and Y is $NHR^{11'}$, NCO or $NR^{11'}COW$;
(x) X is $C(=O)R^6$ and Y is $NHR^{11'}$ or X is $NHR^{11'}$ and Y is $C(=O)R^8$ and n=1;
(xi) X is $NHR^{11'}$ and Y is CR^8R^9W and n=1;
(xii) X is CR^6R^7W and Y is $NHR^{11'}$ or OH and n=1; or
(xiii) X is $CR^6R^7SO_2W$ and Y is H and n=0;
(xiv) X is W or OH and Y is CH_2OH and n is 1;
(xv) X is $NHR^{11'}$ and Y is SO_2W or X is $NR^{11'}SO_2W$ and Y is H, and n is 0;
(xvi) X is $NR^{11'}COCH_2W$ and Y is H and n=0;

in which W is a leaving group, e.g. halo or imidazolyl; R^x and R^y are (C_{1-6})alkyl; R^z is aryl or (C_{1-6})alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);
and thereafter optionally or as necessary converting Q^1 and Q^2 to $NR^{2'}R^{4'}$; converting A', $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $NR^{11'}$ to A, Z^1, Z^2, Z^3, Z^4, Z^5, R^1, R^2, R^3, R^4 and $NR^{11'}$; converting A-B to other A-B, interconverting R^1, R^2, R^3 and/or R^4, and/or forming a pharmaceutically acceptable derivative thereof.

Process variant (i) initially produces compounds of formula (I) wherein A-B is A'-CO.

Process variant (ii) initially produces compounds of formula (I) wherein A-B is CHR^6-CR^8R^9.

Process variant (iii) initially produces compounds of formula (I) wherein A-B is $CR^6(OH)$-CR^8R^9.

Process variant (iv) initially produces compounds of formula (I) where A-B is NH-CO.

Process variant (v) initially produces compounds of formula (I) wherein A-B is CO-CH_2 or CH_2-CO.

Process variant (vi) initially produces compounds of formula (I) wherein A-B is CR^6R^7-CR^8OH.

Process variant (vii) and (viii) initially produce compounds of formula (I) wherein A-B is CR^7=CR^9.

Process variant (ix) initially produces compounds of formula (I) where A-B is CO-NR^{11} or NR^{11}-CO.

Process variant (x) initially produces compounds of formula (I) wherein A-B is NR^{11}-CHR^8.

Process variant (xi) initially produces compounds of formula (I) wherein A-B is $NR^{11'}$-CR^8R^9.

Process variant (xii) initially produces compounds of formula (I) wherein A-B is CR^6R^7- $NR^{11'}$ or CR^6R^7-O.

Process variant (xiii) initially produces compounds of formula (I) where A-B is CR^6R^7-SO_2.

Process variant (xiv) initially produces compounds of formula (I) wherein A-B is O-CH_2.

Process variant (xv) initially produces compounds where AB is $NR^{11}SO_2$.

Process variant (xvi) initially produces compounds of formula (I) where A-B is $NR^{11'}$-CO and n=1.

In process variants (i) and (ix) the reaction is a standard amide or urea formation reaction involving e.g.:

1. Activation of a carboxylic acid (e.g. to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), and treatment with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid and amide are preferably reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-

ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT) or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU); or

2. The specific methods of:

a. *in situ* conversion of an acid into the amine component by a modified Curtius reaction procedure (Shioiri, T., Murata, M., Hamada, Y., *Chem. Pharm. Bull.* 1987, 35, 2698)

b. *in situ* conversion of the acid component into the acid chloride under neutral conditions (Villeneuve, G. B.; Chan, T. H., *Tetrahedron. Lett.* 1997, 38, 6489).

A' may be, for example. protected hydroxymethylene.

The process variant (ii) is a standard addition reaction using methods well known to those skilled in the art. The process is preferably carried out in a polar organic solvent e.g. acetonitrile in the presence of an organic base e.g. triethylamine.

In process variant (iii) the coupling may be effected in acetonitrile at room temperature in the presence of one equivalent of lithium perchlorate as catalyst (general method of J.E. Chateauneuf *et al, J. Org. Chem.*, 56, 5939-5942, 1991) or more preferably with ytterbium triflate in dichloromethane. In some cases an elevated temperature such as 40 – 70 °C may be beneficial. Alternatively, the piperidine may be treated with a base, such as one equivalent of butyl lithium, and the resulting salt reacted with the oxirane in an inert solvent such as tetrahydrofuran, preferably at an elevated temperature such as 80°C. Use of a chiral epoxide will afford single diastereomers. Alternatively, mixtures of diastereomers may be separated by preparative HPLC or by conventional resolution through crystallisation of salts formed from chiral acids.

The process variant (iv) is a standard urea formation reaction from the reaction of an isocyanate with an amine and is conducted by methods well known to those skilled in the art (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p802-3). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide.

In process variant (v) the process is two step: firstly a condensation using a base, preferably sodium hydride or alkoxide, sodamide, alkyl lithium or lithium dialkylamide, preferably in an aprotic solvent e.g. ether, THF or benzene; secondly, hydrolysis using an inorganic acid, preferably HCl in aqueous organic solvent at 0-100°C. Analogous routes are described in DE330945, EP31753, EP53964 and H. Sargent, J. Am. Chem. Soc. 68, 2688-2692 (1946). Similar Claisen methodology is described in Soszko et. al., Pr.Kom.Mat. Przyr.Poznan.Tow.Przyj.Nauk., (1962), 10, 15.

In process variant (vi) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt, preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C (analogous process in Gutswiller et al. (1978) J. Am. Chem. Soc. 100, 576).

In process variants (vii) and (viii) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g.di- isopropylamide. An analogous method is described in US 3989691 and M.Gates et. al. (1970) J. Amer.Chem.Soc., 92, 205, as well as Taylor et al. (1972) JACS 94, 6218.

In process variant (x) where X or Y is CHO the reaction is a standard reductive alkylation using, e.g., sodium borohydride or sodium triacetoxyborohydride (Gribble, G. W. in *Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)* (John Wiley and Sons, 1995), p 4649).

The process variants (xi) and (xii) are standard alkylation reactions well known to those skilled in the art, for example where an alcohol or amine is treated with an alkyl halide in the presence of a base (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p364-366 and p342-343). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide

In process variant (xiii) the reaction is a standard sulphonamide formation reaction well known to those skilled in the art. This may be e.g. the reaction of a sulphonyl halide with an amine.

In process variant (xiv) where X is W such as halogen, methanesulphonyloxy or trifluoromethanesulphonyloxy, the hydroxy group in Y is preferably converted to an OM group where M is an alkali metal by treatment of an alcohol with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium. Where X is OH, the hydroxy group in Y is activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623). Alternatively the X=O and Y=CH_2OH groups can be reacted directly by activation with dichlorocarbodiimide (DCC) (Chem. Berichte 1962, 95, 2997 or Angewante Chemie 1963 75, 377).

In process variant (xv) the reaction is conducted in the presence of an organic base such as triethylamine or pyridine such as described by Fuhrman et.al., J. Amer. Chem. Soc.; 67, 1245, 1945. The X=$NR^{11'}SO_2W$ or Y=SO_2W intermediates can be formed from the requisite amine e.g. by reaction with SO_2Cl_2 analogously to the procedure described by the same authors Fuhrman et.al., J. Amer. Chem. Soc.; 67, 1245, 1945.

In process variant (xvi) the reaction is an alkylation, examples of which are described in J. Med. chem. (1979) 22(10) 1171-6. The compound of formula (IV) may be prepared from the corresponding compound where X is $NHR^{11'}$ by acylation with an appropriate derivative of the acid WCH_2COOH such as the acid chloride.

Reduction of a carbonyl group A or B to CHOH can be readily accomplished using reducing agents well known to those skilled in the art, e.g. sodium borohydride in aqueous ethanol or lithium aluminium hydride in ethereal solution. This is analogous to

methods described in EP53964, US384556 and J. Gutzwiller *et al, J. Amer. Chem. Soc.*, 1978, 100, 576.

The carbonyl group A or B may be reduced to CH_2 by treatment with a reducing agent such as hydrazine in ethylene glycol, at e.g. 130-160°C, in the presence of potassium hydroxide.

Reaction of a carbonyl group A or B with an organometallic reagent yields a group where R^8 is OH and R^9 is alkyl.

A hydroxy group on A or B may be oxidised to a carbonyl group by oxidants well known to those skilled in the art, for example, manganese dioxide, pyridinium chlorochromate or pyridinium dichromate.

A hydroxyalkyl A-B group CHR^7CR^9OH or $CR^7(OH)CHR^9$ may be dehydrated to give the group $CR^7=CR^9$ by treatment with an acid anhydride such as acetic anhydride.

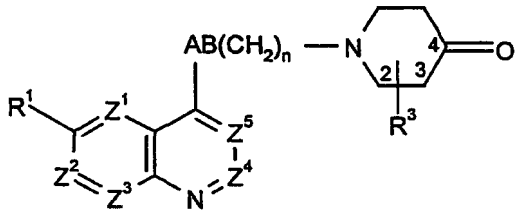
Methods for conversion of $CR^7=CR^9$ by reduction to CHR^7CHR^9 are well known to those skilled in the art, for example using hydrogenation over palladium on carbon as catalyst. Methods for conversion of $CR^7=CR^9$ to give the A-B group $CR^7(OH)CHR^9$ or CHR^7CR^9OH are well known to those skilled in the art for example by epoxidation and subsequent reduction by metal hydrides, hydration, hydroboration or oxymercuration.

An amide carbonyl group may be reduced to the corresponding amine using a reducing agent such as lithium aluminium hydride.

A hydroxy group in A or B may be converted to azido by activation and displacement e.g. under Mitsunobu conditions using hydrazoic acid or by treatment with diphenylphosphorylazide and base, and the azido group in turn may be reduced to amino by hydrogenation.

An example of a group Q^1 convertible to NR^2R^4 is $NR^{2'}R^{4'}$ or halogen. Halogen may be displaced by an amine $HNR^{2'}R^{4'}$ by a conventional alkylation.

When Q^1 Q^2 together form a protected oxo group this may be an acetal such as ethylenedioxy which can subsequently be removed by acid treatment to give a compound of formula (VI):



(VI)

wherein the variables are as described for formula (I)

Intermediates of formula (VI) are novel and as such form part of the invention.

The ketone of formula (VI) is reacted with an amine $HNR^{2'}R^{4'}$ by conventional reductive alkylation as described above for process variant (x).

Examples of groups $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$ convertible to Z^1, Z^2, Z^3, Z^4 and Z^5 include $CR^{1a'}$ where $R^{1a'}$ is a group convertible to R^{1a}. $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$ and $Z^{5'}$ are preferably Z^1, Z^2, Z^3, Z^4 and Z^5.

$R^{1a'}$, $R^{1'}$ and $R^{2'}$ are preferably R^{1a}, R^1 and R^2. $R^{1'}$ is preferably methoxy. $R^{2'}$ is preferably hydrogen. $R^{3'}$ is R^3 or more preferably hydrogen, vinyl, alkoxycarbonyl or carboxy. $R^{4'}$ is R^4 or more preferably H or an N-protecting group such as t-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethyloxycarbonyl.

Conversions of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ and interconversions of R^1, R^2, R^3 and R^4 are conventional. In compounds which contain an optionally protected hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups. N-protecting groups are removed by conventional methods.

For example $R^{1'}$ methoxy is convertible to $R^{1'}$ hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland *et al, J. Amer. Chem. Soc.*, 1973, 7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide and a protected amino, piperidyl, amidino or guanidino group or group convertible thereto, yields, after conversion/deprotection, R^1 alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino.

R^3 alkenyl is convertible to hydroxyalkyl by hydroboration using a suitable reagent such as 9-borabicyclo[3.3.1]nonane, epoxidation and reduction or oxymercuration.

R^3 1,2-dihydroxyalkyl can be prepared from $R^{3'}$ alkenyl using osmium tetroxide or other reagents well known to those skilled in the art (see Advanced Organic Chemistry, *Ed. March, J.*, John Wiley and Sons, 1985, p 732-737 and refs. cited therein) or epoxidation followed by hydrolysis (see Advanced Organic Chemistry, *Ed. March, J.* John Wiley and Sons, 1985, p 332,333 and refs. cited therein).

R^3 vinyl can be chain extended by standard homologation, e.g. by conversion to hydroxyethyl followed by oxidation to the aldehyde, which is then subjected to a Wittig reaction.

Opening an epoxide-containing $R^{3'}$ group with cyanide anion yields a $CH(OH)-CH_2CN$ group.

Opening an epoxide-containing $R^{3'}$ group with azide anion yields an azide derivative which can be reduced to the amine. Conversion of the amine to a carbamate is followed by ring closure with base to give the 2-oxo-oxazolidinyl containing R^3 group.

Substituted 2-oxo-oxazolidinyl containing R^3 groups may be prepared from the corresponding aldehyde by conventional reaction with a glycine anion equivalent, followed by cyclisation of the resulting amino alcohol (M. Grauert *et al, Ann. Chem.*, 1985, 1817; Rozenberg *et al, Angew. Chem. Int. Ed. Engl.*, 1994, 33(1), 91). The resulting 2-oxo-oxazolidinyl group contains a carboxy group which can be converted to other R^{10} groups by standard procedures.

Carboxy groups within R^3 may be prepared by Jones' oxidation of the corresponding alcohols CH_2OH using chromium acid and sulphuric acid in water/methanol (E.R.H. Jones *et al, J. Chem. Soc.*, 1946, 39). Other oxidising agents may be used for this transformation such as sodium periodate catalysed by ruthenium trichloride (G.F. Tutwiler *et al, J. Med. Chem.*, 1987, *30*(6), 1094), chromium trioxide-pyridine (G. Just *et al, Synth. Commun.*, 1979, *9*(7), 613), potassium permanganate (D.E. Reedich *et al, J. Org. Chem.*,1985, 50(19), 3535), and pyridinium chlorochromate (D. Askin *et al, Tetrahedron Lett.*, 1988, 29(3), 277).

The carboxy group may alternatively be formed in a two stage process, with an initial oxidation of the alcohol to the corresponding aldehyde using for instance dimethyl sulphoxide activated with oxalyl chloride (N.Cohen *et al*, J. Am. Chem. Soc., 1983, 105, 3661) or dicyclohexylcarbodiimide (R.M.Wengler, Angew. Chim. Int. Ed. Eng., 1985, 24(2), 77), or oxidation with tetrapropylammonium perruthenate (Ley *et al*, J. Chem.Soc. Chem Commun.,1987, 1625). The aldehyde may then be separately oxidised to the corresponding acid using oxidising agents such as silver (II) oxide (R.Grigg *et al*, J. Chem. Soc. Perkin1,1983, 1929), potassium permanganate (A.Zurcher, Helv. Chim. Acta., 1987, 70 (7), 1937), sodium periodate catalysed by ruthenium trichloride (T.Sakata *et al*, Bull. Chem. Soc. Jpn., 1988, 61(6), 2025), pyridinium chlorochromate (R.S.Reddy *et al*, Synth. Commun., 1988, 18(51), 545) or chromium trioxide (R.M.Coates *et al*, J. Am. Chem. Soc.,1982, 104, 2198).

An R^3 CO_2H group may also be prepared from oxidative cleavage of the corresponding diol, $CH(OH)CH_2OH$, using sodium periodate catalysed by ruthenium trichloride with an acetontrile-carbontetrachloride-water solvent system (V.S.Martin *et al*, Tetrahedron Letters, 1988, *29*(22), 2701).

Other routes to the synthesis of carboxy groups within R^3 are well known to those skilled in the art.

R^3 groups containing a cyano or carboxy group may be prepared by conversion of an alcohol to a suitable leaving group such as the corresponding tosylate by reaction with para-toluenesulphonyl chloride (M.R. Bell, *J. Med. Chem.*,1970, 13, 389), or the iodide using triphenylphosphine, iodine, and imidazole (G. Lange, *Synth. Commun.*, 1990, 20, 1473). The second stage is the displacement of the leaving group with cyanide anion

(L.A. Paquette *et al, J. Org. Chem.*,1979, 44(25), 4603; P.A. Grieco *et al, J. Org. Chem.*, 1988, 53(16), 3658. Finally acidic hydrolysis of the nitrile group gives the desired acids (H.Rosemeyer et al, Heterocycles, 1985, 23 (10), 2669). The hydrolysis may also be carried out with base e.g. potassium hydroxide (H.Rapoport, J. Org. Chem.,1958, 23, 248) or enzymatically (T. Beard et al, Tetrahedron Asymmetry, 1993, 4 (6), 1085).

Other functional groups in R^3 may be obtained by conventional conversions of carboxy or cyano groups.

Tetrazoles are conveniently prepared by reaction of sodium azide with the cyano group (e.g. F. Thomas *et al, Bioorg. Med. Chem. Lett.*, 1996, 6(6), 631; K. Kubo *et al, J. Med. Chem.*, 1993, 36, 2182) or by reaction of azidotri-n-butyl stannane with the cyano group followed by acidic hydrolysis (P.L. Ornstein, *J. Org. Chem.*, 1994, 59, 7682 and *J. Med. Chem*, 1996, 39 (11), 2219).

The 3-hydroxy-3-cyclobutene-1,2-dion-4-yl group (e.g. R.M. Soll, *Bioorg. Med. Chem. Lett.*, 1993, 3(4), 757 and W.A. Kinney, *J. Med. Chem.*, 1992, 35(25), 4720) can be prepared by the following sequence:- (1) a compound where R^3 is $(CH_2)_nCHO$ (n = 0,1,2) is treated with triethylamine, carbon tetrabromide-triphenylphosphine to give initially $(CH_2)_nCH{=}CHBr$; (2) dehydrobromination of this intermediate to give the corresponding bromoethyne derivative $(CH_2)_nC{\equiv}CBr$ (for this 2 stage sequence see D. Grandjean *et al, Tetrahedron Lett.*, 1994, 35(21), 3529); (3) palladium-catalysed coupling of the bromoethyne with 4-(1-methylethoxy)-3-(tri-n-butylstannyl)cyclobut-3-ene-1,2-dione (Liebeskind *et al, J. Org. Chem.*, 1990, 55, 5359); (4) reduction of the ethyne moiety to $-CH_2CH_2-$ under standard conditions of hydrogen and palladium on charcoal catalysis(see Howard *et al, Tetrahedron*, 1980, 36, 171); and finally (4) acidic hydrolysis of the methyl ethoxyester to generate the corresponding 3-hydroxy-3-cyclobutene-1,2-dione group (R.M. Soll, *Bioorg. Med. Chem. Lett.*, 1993, 3(4), 757).

The tetrazol-5-ylaminocarbonyl group may be prepared from the corresponding carboxylic acid and 2-aminotetrazole by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P.L. Ornstein *et al, J. Med Chem*, 1996, 39(11), 2232).

The alkyl- and alkenyl-sulphonylcarboxamides are similarly prepared from the corresponding carboxylic acid and the alkyl- or alkenyl-sulphonamide by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P.L. Ornstein *et al, J. Med. Chem.*, 1996, 39(11), 2232).

The hydroxamic acid groups are prepared from the corresponding acids by standard amide coupling reactions e.g. N.R. Patel *et al, Tetrahedron*, 1987, 43(22), 5375.

2,4-Thiazolidinedione groups may prepared from the aldehydes by condensation with 2,4-thiazolidinedione and subsequent removal of the olefinic double bond by hydrogenation.

The preparation of 5-oxo-1,2,4-oxadiazoles from nitriles is decribed by Y. Kohara *et al, Bioorg. Med. Chem. Lett.*, 1995, 5(17), 1903.

1,2,4-Triazol-5-yl groups may be prepared from the corresponding nitrile by reaction with an alcohol under acid conditions followed by reaction with hydrazine and then an R^{10}-substituted activated carboxylic acid (see J.B. Polya in "Comprehensive Heterocyclic Chemistry" Edition 1, p762, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984 and J.J. Ares *et al, J. Heterocyclic Chem.*, 1991, 28(5), 1197).

Other substituents on R^3 alkyl or alkenyl may be interconverted by conventional methods, for example hydroxy may be derivatised by esterification, acylation or etherification. Hydroxy groups may be converted to halogen, thiol, alkylthio, azido, alkylcarbonyl, amino, aminocarbonyl, oxo, alkylsulphonyl, alkenylsulphonyl or aminosulphonyl by conversion to a leaving group and substitution by the required group or oxidation as appropriate or reaction with an activated acid, isocyanate or alkoxyisocyanate. Primary and secondary hydroxy groups can be oxidised to an aldehyde or ketone respectively and alkylated with a suitable agent such as an organometallic reagent to give a secondary or tertiary alcohol as appropriate.

An NH_2 substituent on piperidine is converted to NR^2R^4 by conventional means such as amide or sulphonamide formation with an acyl derivative X^4-X^3-X^2-COW or X^4-X^3-X^2-SO_2W, for compounds where U is CO or SO_2 or, where U is CH_2, alkylation with an alkyl halide R^4-halide in the presence of base, acylation/reduction with an acyl derivative X^4-X^3-X^2-COW or reductive alkylation with an aldehyde X^4-X^3-X^2-CHO.

Where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage. This linkage may form spontaneously during coupling of the compound of formula (IV) and the piperidine moiety or in the presence of standard peptide coupling agents.

Examples of $R^{4'}$ convertible to R^4 include $-CH_2$-CO_2H which may be reacted with an amine X^4-NH_2 in the presence of a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) to give R^4=X^4-NH-CO-CH_2-. This reaction may be carried out on the compound of formula (V) or after coupling (IV) and (V). Cyclisation of the hydroxy and amino (R^{14} and R^{13}) groups may be effected with phosgene in base.

Interconversion of substituents on the aromatic group X^4 may be carried out conventionally at any appropriate point in the synthesis. For example pyridine may be

oxidised to the the N-oxide with and oxidising agent such as meta-chloroperbenzoic acid, hydrogen peroxide or t-butyl hydroperoxide after protection of any other nitrogen atoms. N-oxides may be rearranged in trifluoroacetic acid to give the hydroxypyridines.

It will be appreciated that under certain circumstances interconversions may interfere, for example, hydroxy groups in A or B and the piperidine substituent NH_2 will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for piperidine NH_2, during conversion of $R^{1'}$, $R^{2'}$, $R^{3'}$ or $R^{4'}$, or during the coupling of the compounds of formulae (IV) and (V).

Compounds of formulae (IV) and (V) are known compounds, (see for example Smith *et al, J. Amer. Chem. Soc.*, 1946, 68, 1301) or prepared analogously.

Compounds of formula (IV) where X is $CR^6R^7SO_2W$ may be prepared by a route analogous to that of Ahmed El Hadri *et al, J. Heterocyclic Chem.*, 1993, 30(3), 631. Thus compounds of formula (IV) where X is CH_2SO_2OH may be prepared by reacting the corresponding 4-methyl compound with N-bromosuccinimide, followed by treatment with sodium sulfite. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods.

The isocyanate of formula (IV) may be prepared conventionally from a 4-amino derivative such as 4-amino-quinoline, and phosgene, or phosgene equivalent (eg triphosgene) or it may be prepared more conveniently from a 4-carboxylic acid by a "one-pot" Curtius Reaction with diphenyl phosphoryl azide (DPPA) [see T. Shiori et al. *Chem. Pharm. Bull.* **35**, 2698-2704 (1987)].

The 4-amino derivatives are commercially available or may be prepared by conventional procedures from a corresponding 4-chloro or 4-trifluoromethanesulphonate derivative by treatment with ammonia (O.G. Backeberg et. al., J. Chem Soc., 381, 1942) or propylamine hydrochloride (R. Radinov et. al., Synthesis, 886, 1986).

4-Alkenyl compounds of formula (IV) may be prepared by conventional procedures from a corresponding 4-halogeno-derivative by e.g. a Heck synthesis as described in e.g. *Organic Reactions*, 1982, 27, 345.

4-Halogeno derivatives of compounds of formula (IV) are commercially available, or may be prepared by methods known to those skilled in the art. A 4-chloroquinoline is prepared from the corresponding quinolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5. A 4-chloroquinazoline is prepared from the corresponding quinazolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride PCl_5. A quinazolinone and quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield.

Activated carboxy derivatives X=A'COW of formula (IV) may be prepared from X=A'CO_2H derivatives in turn prepared from CO_2H derivatives by conventional methods such as homologation.

4-Carboxy derivatives of compounds of formula (IV) are commercially available or ma be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art. For example, quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield. These 4-carboxy derivatives may be activated by conventional means, e.g. by conversion to an acyl halide or anhydride.

4-Carboxy derivatives such as esters may be reduced to hydroxymethyl derivatives with for example lithium aluminium hydride. Reaction with mesyl chloride and triethylamine would give the mesylate derivative.

A 4-oxirane derivative of compounds of formula (IV) is conveniently prepared from the 4-carboxylic acid by first conversion to the acid chloride with oxalyl chloride and then reaction with trimethylsilyldiazomethane to give the diazoketone derivative. Subsequent reaction with 5M hydrochloric acid gives the chloromethylketone. Reduction with sodium borohydride in aqueous methanol gives the chlorohydrin which undergoes ring closure to afford the epoxide on treatment with base, e.g. potassium hydroxide in ethanol-tetrahydrofuran.

Alternatively and preferably, 4-oxirane derivatives can be prepared from bromomethyl ketones which can be obtained from 4-hydroxy compounds by other routes well known to those skilled in he art. For example, hydroxy compounds can be converted to the corresponding 4-trifluoromethanesulphonates by reaction with trifluoromethanesulphonic anhydride under standard conditions (see K. Ritter, Synthesis, 1993, 735). Conversion into the corresponding butyloxyvinyl ethers can be achieved by a Heck reaction with butyl vinyl ether under palladium catalysis according to the procedure of W. Cabri *et al,* J. Org. Chem, 1992, **57** (5), 1481. (Alternatively, the same intermediates can be attained by Stille coupling of the trifluoromethanesulphonates or the analogous chloro derivatives with (1-ethoxyvinyl)tributyl tin, T. R. Kelly, J. Org. Chem., 1996, **61**, 4623.) The alkyloxyvinyl ethers are then converted into the corresponding bromomethylketones by treatment with N-bromosuccinimide in aqueous tetrahydrofuran in a similar manner to the procedures of J. F. W. Keana, J. Org. Chem., 1983, **48**, 3621 and T. R. Kelly, J. Org. Chem., 1996, **61**, 4623.

The 4-hydroxyderivatives can be prepared from an aminoaromatic by reaction with methylpropiolate and subsequent cyclisation, analogous to the method described in N. E. Heindel et al, J. Het. Chem., 1969, **6**, 77. For example, 5-amino-2-methoxy pyridine can be converted to 4-hydroxy-6-methoxy-[1,5]naphthyridine using this method.

If a chiral reducing agent such as (+) or (-)-B-chlorodiisopinocamphenylborane ['DIP-chloride'] is substituted for sodium borohydride, the prochiral chloromethylketone is converted into the chiral chlorohydrin with ee values generally 85-95% [see C. Bolm *et al, Chem. Ber.* 125, 1169-1190, (1992)]. Recrystallisation of the chiral epoxide gives material in the mother liquor with enhanced optical purity (typically ee 95%).

The *(R)*-epoxide, when reacted with a piperidine derivative gives ethanolamine compounds as single diastereomers with *(R)*-stereochemistry at the benzylic position.

Alternatively, the epoxide may be prepared from the 4-carboxaldehyde by a Wittig approach using trimethylsulfonium iodide [see G.A. Epling and K-Y Lin, *J. Het. Chem.*, 1987, 24, 853-857], or by epoxidation of a 4-vinyl derivative.

Pyridazines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 3, Ed A.J. Boulton and A. McKillop and napthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

4-Hydroxy-1,5-naphthyridines can be prepared from 3-aminopyridine derivatives by reaction with diethyl ethoxymethylene malonate to produce the 4-hydroxy-3-carboxylic acid ester derivative with subsequent hydrolysis to the acid, followed by thermal decarboxylation in quinoline (as for example described for 4-Hydroxy-[1,5]naphthyridine-3-carboxylic acid, J. T. Adams *et al., J.Amer.Chem.Soc.*, 1946, **68**, 1317). A 4-hydroxy-[1,5]naphthyridine can be converted to the 4-chloro derivative by heating in phosphorus oxychloride, or to the 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with methanesulphonyl chloride or trifluoromethanesulphonic anhydride, respectively, in the presence of an organic base. A 4-amino 1,5-naphthyridine can be obtained from the 4-chloro derivative by reaction with n-propylamine in pyridine.

Similarly, 6-methoxy-1,5-naphthyridine derivatives can be prepared from 3-amino-6-methoxypyridine.

1,5-Naphthyridines may be prepared by other methods well known to those skilled in the art (for examples see P.A. Lowe in "Comprehensive Heterocyclic Chemistry" Volume 2, p581-627, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984).

The 4-hydroxy and 4-amino-cinnolines may be prepared following methods well known to those skilled in the art [see A.R. Osborn and K. Schofield, *J. Chem. Soc.* 2100 (1955)]. For example, a 2-aminoacetopheneone is diazotised with sodium nitrite and acid to produce the 4-hydroxycinnoline with conversion to chloro and amino derivatives as described for 1,5-naphthyridines.

The compounds of formula (V) are either commercially available or may be prepared by conventional methods.

For compounds of formula (V), suitable amines (Q^1 = NH2 and Q^2 = H) may be prepared from the corresponding 4-substituted piperidine acid or alcohol. In a first instance, an N-protected piperidine containing an acid bearing substituent, can undergo a Curtius rearrangement and the intermediate isocyanate can be converted to a carbamate by reaction with an alcohol. Conversion to the amine may be achieved by standard methods well known to those skilled in the art used for amine protecting group removal. For example, an acid substituted N-protected piperidine can undergo a Curtius rearrangement e.g. on treatment with diphenylphosphoryl azide and heating, and the intermediate isocyanate reacts in the presence of 2-trimethylsilylethanol to give the trimethylsilylethylcarbamate (T.L. Capson & C.D. Poulter, *Tetrahedron Lett.*, 1984, 25, 3515). This undergoes cleavage on treatment with tetrabutylammonium fluoride to give the 4-amine substituted N-protected piperidine.

In a second instance, an N-protected piperidine containing an alcohol bearing substituent undergoes a Mitsunobu reaction (for example as reviewed in Mitsunobu, *Synthesis*, (1981), 1), for example with succinimide in the presence of diethyl azodicarboxylate and triphenylphosphine to give the phthalimidoethylpiperidine. Removal of the phthaloyl group, for example by treatment with methylhydrazine, gives the amine of formula (V).

Compounds of formula (V) containing an $R^{3'}$ in the 4-position may be made from the corresponding 4-amino, 4-alkoxycarbonyl piperidine derivative from the commercially available acid. Standard transformations on this ester or acid yield the required $R^{3'}$ group.

Addition of YCH_2 to piperidine may be via standard alkylations using for example an alkyl halide such as YCH_2Br or reductive alkylation with an aldehyde YCHO. Addition of acyl groups Y to piperidine eg carbonyl or sulphonyl may be carried out by conventional amide/sulponamide formation.

R^4-halides, acyl derivative X^4-X^3-X^2-COW and X^4-X^3-X^2-SO_2W or aldehydes X^4-X^3-X^2-CHO are commercially available or are prepared conventionally. The aldehydes may be prepared by partial reduction of the corresponding ester (see *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed., Wiley, N.Y., 1997; *JOC*, 3197, 1984; *Org. Synth. Coll.*, 102, 1990; 136, 1998; *JOC*, 4260, 1990; *TL*, 995, 1988; *JOC*, 1721, 1999; *Liebigs Ann./Recl.*, 2385, 1997; *JOC*, 5486, 1987).with lithium aluminium hydride or di-isobutylaluminium hydride or more preferably by reduction to the alcohol, with lithium aluminium hydride or sodium borohydride, followed by oxidation to the aldehyde with manganese (II) dioxide. The aldehydes may also be prepared from carboxylic acids in two stages by conversion to a mixed anhydride

for example by reaction with isobutyl chloroformate followed by reduction with sodium borohydride (R. J. Alabaster et al., Synthesis, 598, 1989) to give the benzylic alcohols and then oxidation with a standard oxidising agent such as pyridinium dichromate or manganese (II) dioxide. Acyl derivative may be prepared by activation of the corresponding ester. R^4-halides such as bromides may be prepared from the alcohol R^4OH by reaction with phosphorus tribromide in DCM/triethylamine. Where X^2 is CO and X^3 is NR^{13} the R^4-halide may be prepared by coupling an X^4-NH_2 amine and bromoacetyl bromide.

The amines $R^{2'}R^{4'}NH$ are available commercially or prepared conventionally. For example amines X^4-X^3-X^2-CH_2NH_2 may be prepared from a bromomethyl derivative by reaction with sodium azide in dimethylformamide (DMF), followed by hydrogenation of the azidomethyl derivative over palladium-carbon. An alternative method is to use potassium phthalimide/DMF to give the phthalimidomethyl derivative, followed by reaction with hydrazine in DCM to liberate the primary amine. Amines where X^2 is CO and X^3 is NR^{13} may be prepared by reacting an N-protected glycine derivative HO_2C-X^1-NH_2 with X^4-NH_2 by conventional coupling using eg EDC.

Conversions of $R^{1a'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ may be carried out on the intermediates of formulae (IV), and (V) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable derivatives thereof.

Novel intermediates of formulae (IV) and (V) are also part of this invention.

The antibacterial compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibacterials.

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The composition may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be

frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable derivative thereof is administered in the above-mentioned dosage range.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibacterials. If the other antibacterial is a β-lactam then a β-lactamase inhibitor may also be employed.

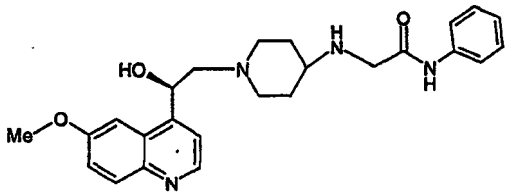
Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

EXAMPLES

Example 1. 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-phenyl-acetamide dioxalate



(a) [R]-2-(6-Methoxyquinolin-4-yl)oxirane

A solution of 6-methoxyquinoline-4-carboxylic acid (10g) in dichloromethane was heated under reflux with oxalyl chloride (5ml) and dimethylformamide (2 drops) for 1 hour and evaporated to dryness. The residue, in dichloromethane (100ml) was treated with a 2M solution of trimethylsilyldiazomethane in hexane (50ml) and stirred at room temperature for 18 hours. 5M Hydrochloric acid (150ml) was added and the solution was stirred at room temperature for 3 hours. It was basified with sodium carbonate solution, extracted with ethyl acetate and chromatographed on silica gel eluting with ethyl acetate-hexane to give the chloromethyl ketone (4.2g). A batch of the chloromethyl ketone (20g) was reduced with (+)-B-chlorodiisopinocamphenylborane (40g) in dichloromethane (400ml) at room temperature for 18 hours followed by treatment with diethanolamine (30 g) for 3 hours. The product was chromatographed on silica gel eluting with ethyl acetate-hexane to give the chloroalcohol (16.8g), which was dissolved in tetrahydrofuran (100 ml) and reacted with sodium hydroxide (2.6g) in water (13ml) for 1.5 hours. The reaction mixture was evaporated to dryness and chromatographed on silica gel eluting with ethyl acetate - hexane to give the title compound as a solid (10.4 g) (84% ee by chiral HPLC). Recrystallisation from ether-pentane gave mother-liquor (7.0 g) (90% ee).

MS (+ve ion electrospray) m/z 202 (MH+)

The absolute stereochemistry was defined to be (R) by an NMR study on the Mosher's esters derived from the product obtained by reaction with 1-t-butylpiperazine.

(b) 1-[2-(R)-Hydroxy-2-(6-methoxyquinolin-4-yl)]ethyl-4-oxo piperidine, ethylene ketal.

[R]-2-(6-Methoxyquinolin-4-yl)oxirane (1a) (470 mg) and 1,4-dioxa-8-azaspiro-[4,5]-decane (0.33 ml) were dissolved in dry dichloromethane (5 ml) and ytterbium triflate (30 mol%) was added. The mixture was stirred for 6 hours, filtered through celite, evaporated and chromatographed on silica gel (dichloromethane then methanol-dichloromethane).

MS (+ve ion electrospray) m/z 345 (MH+).

(c) 4-Oxo-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine.

The ketal (1b) was cleaved by treatment with 5M HCl (10 ml) in acetone (20 ml) at 60 °C overnight. The mixture was basified with sodium bicarbonate solution and concentrated. Extraction into dichloromethane, evaporation and chromatography on silica gel (dichloromethane then methanol-dichloromethane) gave a yellow gum (482 mg).

(d) Title compound

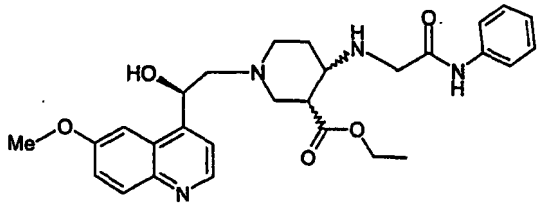
The ketone (1c) (0.113g), 2-amino-N-phenyl acetamide (prepared from N-t-Boc-glycine N-hydroxysuccinimide ester and aniline followed by deprotection in trifluoroacetic acid-dichloromethane) (0.065g) and sodium triacetoxyborohydride (0.08g) were added together to dry methanol (2ml), followed by 3A molecular sieves and the mixture was stirred slowly at room temperature for 18 hours. It was filtered, evaporated, and treated with sodium carbonate solution. The mixture was extracted with dichloromethane, dried, evaporated and chromatographed on silica gel (ethyl acetate then methanol-dichloromethane) to afford the title compound (0.093g).

MS (+ve ion electrospray) m/z 435 (MH+).

^{1}H NMR ($CDCl_3$) δ: 1.50–2.90 (10H, m), 3,25 (2H, m), 3.40 (2H, s), 3.95 (3H, s), 5.45 (1H, m) 7.10 (1H, brt), 7.15 (1H, d), 7.30-7.70 (7H, m), 8.05 (1H, d), 8.78 (1H, d), 9.30 (1H, brs).

The free base in dichloromethane was treated with 2 molar equivalents of oxalic acid in ether and the resulting solid was collected, triturated with ether, to afford the dioxalate salt as a white solid.

Example 2. *cis*-2-{1-[2-(R)-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-3-(R/S)-ethoxycarbonyl-piperidin-4-(S/R)-ylamino}-N-phenyl-acetamide dioxalate



(a) 4-Benzylamino-1-tert-butoxycarbonyl-3-ethoxycarbonyl-1,2,5,6-tetrahydropyridine

A solution of 1-*tert*-butoxycarbonyl-3-ethoxycarbonylpiperidin-4-one (prepared from 3-ethoxycarbonylpiperidin-4-one and di-*tert*-butyl-dicarbonate in dichloromethane and triethylamine) (25g) and benzylamine (10.85g) in toluene was heated under reflux in a Dean and Stark apparatus for 18 hours and then evaporated to dryness to give an oil.

(b) *cis*-4-(S/R)-Benzylamino-1-tert-butoxycarbonyl-3-(R/S)-ethoxycarbonylpiperidine

The enamine (2a) (25g) in ethanol (300ml) was hydrogenated over platinum oxide (1.5g) for 4 days, filtered, and evaporated to dryness. It was chromatographed on silica gel (ethyl acetate-hexane) to afford the title compound as an oil.

MS (+ve ion electrospray) m/z 363 (MH^+).

(c) *cis*-4-(S/R)-Amino-1-*tert*-butoxycarbonyl-3-(R/S)-ethoxycarbonylpiperidine

The amine (2b) (4g) in ethanol (80ml) containing acetic acid (0.73g) was hydrogenated at 50psi (Parr reaction vessel) over 10% palladium-carbon (1g) for 18 hours, filtered and evaporated to dryness to afford the acetate salt of the title compound as a white solid (3g).

MS (+ve ion electrospray) m/z 273 (MH+).

It was converted to the oily free base by extraction using dichloromethane-sodium carbonate and drying over sodium sulfate.

(d) *cis*-[1-*tert*-Butoxycarbonyl-3-(R/S)-ethoxycarbonyl-piperidin-4-(S/R)-ylamino]-N-phenyl-acetamide

A solution of the amine (2c) (0.8g) in dry dimethylformamide (5ml) containing anhydrous potassium carbonate (1.5g) was treated with 2-bromo-N-phenylacetamide (0.664g) and the mixture was stirred at room temperature for 18 hours. The mixture was evaporated to dryness, brine was added and the solution was extracted with dichloromethane. The organic fraction was dried, evaporated, and chromatographed on silica gel (ethyl acetate-hexane) to afford an oil (0.82g).

MS (+ve ion electrospray) m/z 406 (MH+).

(e) *cis*-[3-(R/S)-Ethoxycarbonyl-piperidin-4-(S/R)-ylamino]-N-phenyl-acetamide

A solution of the acetamide (2d) (0.81g) in dichloromethane (30ml) was treated with trifluoroacetic acid (30ml) and the solution was left at room temperature for 2.5 hours. It was evaporated to dryness, sodium carbonate solution was added, and it was extracted with chloroform, dried, and evaporated to give an oil (0.6g).

MS (+ve ion electrospray) m/z 306 (MH+).

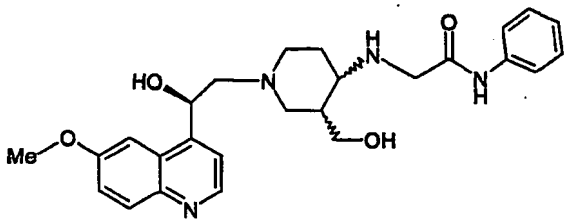
(f) Title compound

A solution of [R]-2-(6-methoxyquinolin-4-yl)oxirane (1a) (0.13g) and the piperidine (2e) (0.197g) in acetonitrile (3ml) containing lithium perchlorate (0.068g) was left at room temperature for 5 days and evaporated to dryness. The product was dissolved in dichloromethane, washed with sodium carbonate, dried over sodium sulfate, and chromatographed on silica gel (ethyl acetate-hexane) to afford a foam (0.162g).

MS (+ve ion electrospray) m/z 507 (MH+).

The free base was treated with 2 molar equivalents of oxalic acid in ether and the resulting solid was collected, triturated with ether, to afford the dioxalate salt as a white solid.

Example 3. *cis*-2-{1-[2-(R)-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-3-(R/S)-hydroxymethyl-piperidin-4-(S/R)-ylamino}-N-phenyl-acetamide dioxalate



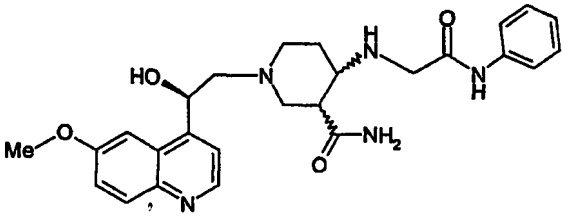
The ester Example (2) (0.095g) in dry tetrahydrofuran (3ml) at 0°C was treated with lithium aluminium hydride (0.36ml of a 1M solution in tetrahydrofuran) for 4 hours and then quenched by the addition of 2M sodium hydroxide. Dichloromethane and sodium sulfate were added and the solution was filtered and evaporated to dryness. The product was chromatographed on silica gel (methanol-dichloromethane) to afford the title compound (0.031g), as the oily free base.

MS (+ve ion electrospray) m/z 464 (MH+).

^{1}H NMR ($CDCl_3$) δ: 1.70–3.10 (10H, m), 3,40 (2H, brs), 3.95 (3H, d), 4.10 (2H,m), 5.45 (1H, m) 7.15 (2H, m), 7.30 (4H, m), 7.60 (3H,m), 8.05 (1H, d), 8.76 (1H, d), 9.15 (1H, brd).

The free base was converted to the dioxalate salt in the normal manner, affording a white solid.

Example 4. *cis*-2-{1-[2-(R)-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-3-(R/S)-aminocarbonyl-piperidin-4-(S/R)-ylamino}-N-phenyl-acetamide dioxalate.



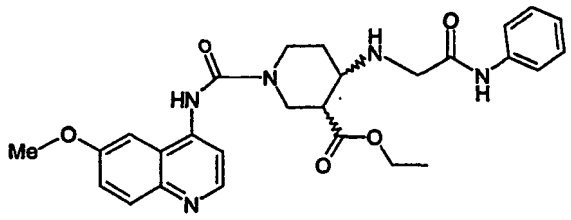
The ester Example (3) (0.035g) in methanol (2ml) was heated with ammonia (2ml) and sodium cyanide (1mg) at 50°C (sealed bomb) for 72 hours and evaporated to dryness. Chromatography on silica gel (ethyl-acetate then methanol-dichloromethane) gave the title compound (0.015g), as the free base.

MS (+ve ion electrospray) m/z 478 (MH+).

^{1}H NMR ($CDCl_3$) δ: 1.60–3.30 (10H, m), 3,50 (2H, m), 3.90 (3H, d), 5.45 (1H, m) 7.15 (2H, m), 7.30 (4H, m), 7.60 (3H,m), 8.0 (1H, m), 8.70 (1H, m), 9.40 (1H, brd).

The free base in dichloromethane-ether was converted to the dioxalate salt in the normal manner, affording a white solid.

Example 5 ***cis*****-3-(R/S)-Ethoxycarbonyl-4-(S/R)-(phenylcarbamoylmethyl-amino)-piperidine-1-carboxylic acid (6-methoxy-quinolin-4-yl)-amide oxalate.**



(a) 4-Amino-6-methoxyquinoline

Curtius rearrangement of 6-methoxyquinoline-4-carboxylic acid (4g, 20mmol) with diphenylphosphoryl azide (4.3ml, 20mmol) and triethylamine(3.5ml) in *tert*-butanol (25ml) at 85°C gave, after chromatography on silica gel (ethyl acetate-dichloromethane) the N-*tert*-butoxycarbamate (2.47g). Treatment with aqueous hydrochloric acid at reflux, followed by basification and extraction with ethyl acetate gave the 4-aminoquinoline (0.74g).

This compound may also be prepared from 4-hydroxy-6-methoxyquinoline by chlorination with phosphorus oxychloride, to give the 4-chloroquinoline, followed by treatment with n-propylamine hydrochloride.

(b) 4-(1-Imidazolylcarbonyl)amino-6-methoxyquinoline

A suspension of 4-amino-6-methoxyquinoline (5a) (2.0g, 11 mmol) in ethanol-free chloroform (60ml) was treated with 4-N,N-dimethylaminopyridine (1.4g, 11.4 mmol) and carbonyl diimidazole (2.6g, 15.9 mmol). The suspension became clear over 1 hour then precipitation occurred. After a further 2 hours, filtration afforded the product as a white solid which was dried *in vacuo* (1.8g, 59%).

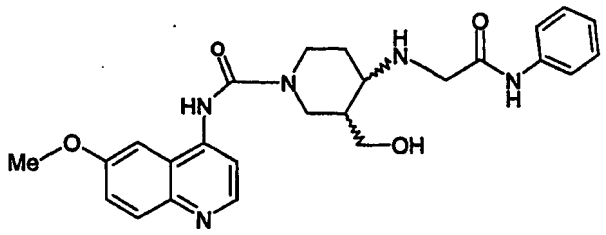
(c) *cis*-3-(R/S)-Ethoxycarbonyl-4-(S/R)-(phenylcarbamoylmethyl-amino)-piperidine-1-carboxylic acid (6-methoxy-quinolin-4-yl)-amide

A solution of 4-(1-imidazolylcarbonyl)amino-6-methoxyquinoline (5b) and amine (2e) (0.211g) in dry DMF (0.5ml) was heated at 50°C for 3 hours and evaporated to dryness. Sodium carbonate and brine were added and the mixture was extracted with dichloromethane, washed with water, dried, evaporated and chromatographed on silica gel (ethyl acetate) to give an oil (0.092g).

MS (+ve ion electrospray) m/z 506 (MH+).

The free base in dichloromethane-ether was converted to the oxalate salt in the normal manner, affording a white solid.

Example 6 ***cis*****-3-(R/S)-Hydroxymethyl-4-(S/R)-(phenylcarbamoylmethyl-amino)-piperidine-1-carboxylic acid (6-methoxy-quinolin-4-yl)-amide oxalate.**



This was prepared from ester Example (5c) (0.096g) by reduction with lithium aluminium hydride by the Method of Example 3 to give an oil (0.031g)
^{1}H NMR ($CDCl_3$) δ: 1.55 (1H, m), 1.85 (1H, m), 2.40 (1H, m), 2.80–3.15 (3H, m), 3.40 (2H, d), 3.75 (2H, brd), 3.85 (3H, s), 4.05 (1H, m), 4.37 (1H, brd), 4.50 (1H, brd), 7.10 (3H, m), 7.15 (1H, d), 7.30 (3H, t), 7.60 (2H, d), 8.05 (1H, d), 8.35 (1H, d), 9.00 (1H, brs).
MS (+ve ion electrospray) m/z 464 (MH+).
The free base in dichloromethane-ether was converted to the oxalate salt in the normal manner, affording a white solid.

The following Examples 7-12 were prepared by the Method of Example 1:

Example7 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-(3-pyridyl)-acetamide dioxalate
MS (+ve ion electrospray) m/z 436 (MH+).

Example 8 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-(4-pyridyl)-acetamide dioxalate
MS (+ve ion electrospray) m/z 436 (MH+).

Example 9 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-(1,3-dimethylpyrazol-5-yl)-acetamide dioxalate
MS (+ve ion electrospray) m/z 453 (MH+).

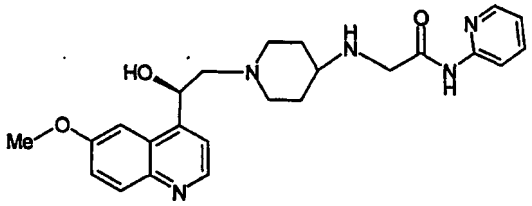
Example 10 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-(1-methylpyrazol-5-yl)-acetamide dioxalate
MS (+ve ion electrospray) m/z 439 (MH+).

Example 11 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-methyl-N-phenyl-acetamide dioxalate
MS (+ve ion electrospray) m/z 449 (MH+).

Example 12 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl-N-methylamino}-N-phenyl-acetamide dioxalate

MS (+ve ion electrospray) m/z 449 (MH+).

Example 13. 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-pyridin-2-yl-acetamide dioxalate



(a) N-(2-Pyridyl)-2-bromo acetamide

To a solution of 2-aminopyridine (0.38 g, 4 mmol) in tetrahydrofuran (7ml) was added triethylamine (0.7ml, 5 mmol) and bromoacetyl bromide (0.44ml, 5 mmol) dropwise. The mixture was shaken overnight and then quenched with sodium bicarbonate solution(20ml). Ethyl acetate (20ml) was added and the layers separated, the organic layer was evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a tan solid (300mg; 35%).

(b) 4-tert-Butoxycarbonylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine.

To a stirred solution of [R]-2-(6-methoxyquinolin-4-yl)oxirane (1a) (8.07g, 40.3 mmol) and lithium perchlorate (4.44g, 40.3 mmol) in anhydrous DMF (100ml) was added 4-*tert*-butoxycarbonylaminopiperidine hydrochloride (11.0g, 45.7 mmol) and potassium carbonate (6.72g, 48.4 mmol). The mixture was heated at 90°C for 26 hours , then cooled, filtered and evaporated. The residue was dissolved in ethyl acetate, washed with water, dried and evaporated. The crude product was chromatographed on silica gel (methanol-dichloromethane) to give a gum (11.11g).

MS (+ve ion electrospray) m/z 402 (MH+).

(c) 4-Amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine.

The *tert*-butoxycarbonylamino compound (13b) (11.11g, 27.7 mmol) was dissolved in dichloromethane (30ml), cooled in ice and treated with trifluoroacetic acid (30ml). The solution was stirred at room temperature for 1.5 hours, then evaporated *in vacuo*. After addition of toluene (50ml) and re-evaporation, the residue was treated with a 4M solution of hydrogen chloride in 1,4-dioxan (30ml). The resulting solid was triturated, filtered off and washed with ether. This was then recrystallised by dissolving in hot methanol, concentrating the solution and diluting with dichloromethane, to give the trihydrochloride salt (9.4g). This was dissolved in water, basified to pH9 and evaporated to dryness. The residue was extracted several times with 10% methanol-dichloromethane

(total 600ml). The extracts were filtered and evaporated to give the free base as a semi-solid foam (6.45g).

MS (+ve ion electrospray) m/z 302 (MH+).

(d) Title compound

N-(2-Pyridyl)-2-bromo acetamide (13a) (55mg, 0.18 mmol) was dissolved in dimethylformamide (2ml). The amine (13c) (55mg, 0.18 mmol) and potassium carbonate (28mg, 0.20 mmol) were added and the mixture was stirred at room temperature for 72 hours and then the solvent was removed *in vacuo*. The residue was partitioned between dichloromethane (10ml) and water (10ml). The layers were separated and the aqueous layer was extracted with a further portion of dichloromethane (10ml). The combined extracts were evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a colorless oil (36mg; 45%).

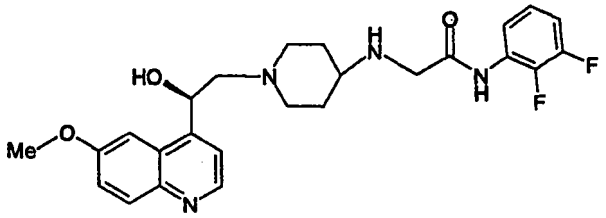
MS (+ve ion electrospray) m/z 436 (MH+).

^{1}H NMR ($CDCl_3$) δ: 1.60 (2H, m), 2.0 (2H, m), 2.15 (1H, m), 2.40 (1H, m), 2.55 (2H, m), 2.85 (2H, m), 3.25 (1H, m), 3.45 (2H, s), 3.90 (3H, s), 5.40 (1H, dd), 7.05 (1H, dt), 7.15 (1H, dt), 7.35 (1H, dd), 7.65 (1H, d), 7.70 (1H, dt), 8.00 (1H, d), 8.25 (1H, d), 8.30 (1H, dd), 8.75 (1H, d), 9.8 (1H, brs)

The oil was treated with oxalic acid in the usual way to give the dioxalate salt.

The following Examples 14-28 were prepared by the Method of Example 13:

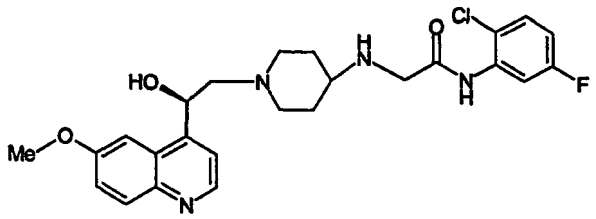
Example 14. N-(2,3-Difluoro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



MS (+ve ion electrospray) m/z 471 (MH+)

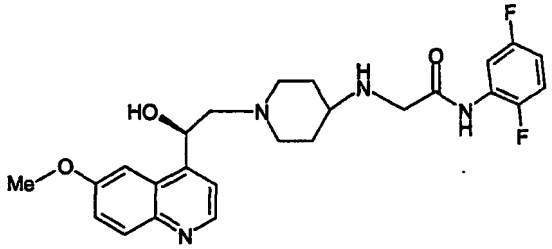
^{1}H NMR ($CDCl_3$) δ: 1.55 (2H, m), 2.0 (2H, m), 2.25 (1H, m), 2.40 (1H, m), 2.55 (2H, m), 2.85 (2H, m), 3.30 (1H, m), 3.45 (2H, s), 3.90 (3H, s), 5.45 (1H, dd), 6.90 (1H, m), 7.10 (1H, m), 7.15 (1H, d), 7.40 (1H, dd), 7.60 (1H, d), 8.00 (1H, d), 8.15 (1H, t), 8.75 (1H, d), 9.85 (1H, brs).

Example 15. N-(2-Chloro-5-fluoro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



MS (+ve ion electrospray) m/z 487 (MH+)

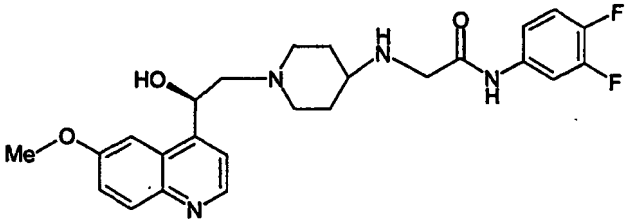
Example 16. N-(2,5-Difluoro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



MS (+ve ion electrospray) m/z 471 (MH+)

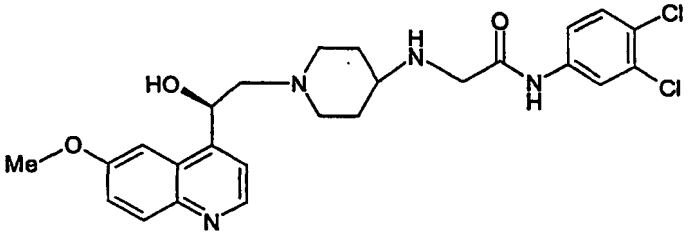
^{1}H NMR ($CDCl_3$) δ: 1.55 (2H, m), 2.0 (2H, m), 2.20 (1H, m), 2.40 (1H, m), 2.55 (2H, m), 2.85 (2H, m), 3.30 (1H, m), 3.45 (2H, s), 3.90 (3H, s), 5.40 (1H, dd), 6.75 (1H, m), 7.00 (1H, m), 7.15 (1H, d), 7.35 (1H, dd), 7.65 (1H, d), 8.00 (1H, d), 8.25 (1H, m), 8.80 (1H, d), 9.85 (1H, brs).

Example 17. N-(3,4-Difluoro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



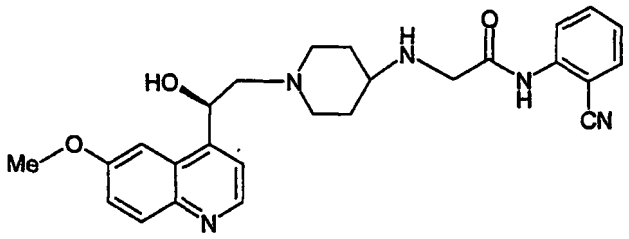
MS (+ve ion electrospray) m/z 471 (MH+)

Example 18. N-(3,4-Dichloro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



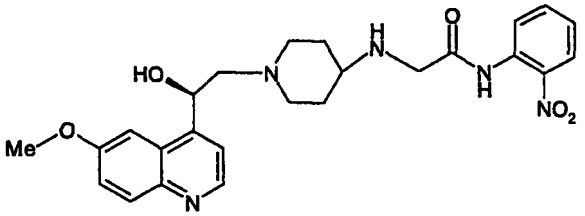
MS (+ve ion electrospray) m/z 503, 505 (MH+)

Example 19. N-(2-Cyano-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



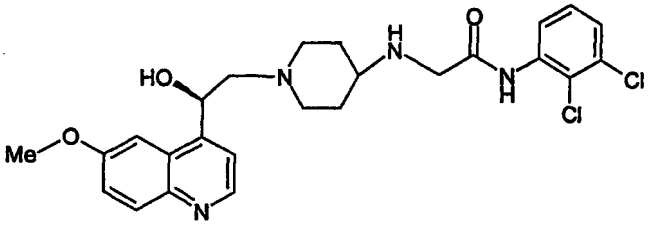
MS (+ve ion electrospray) m/z 460 (MH+)

Example 20. 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-(2-nitro-phenyl)-acetamide dioxalate



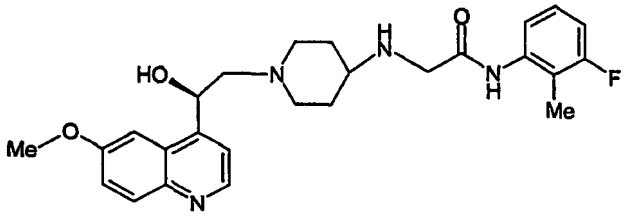
MS (+ve ion electrospray) m/z 480 (MH+)

Example 21. N-(2,3-Dichloro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



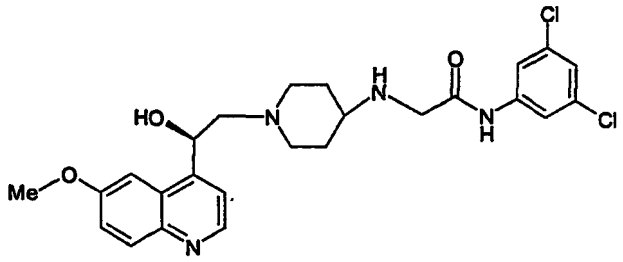
MS (+ve ion electrospray) m/z 503, 505 (MH+)

Example 22. N-(3-Fluoro-2-methyl-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



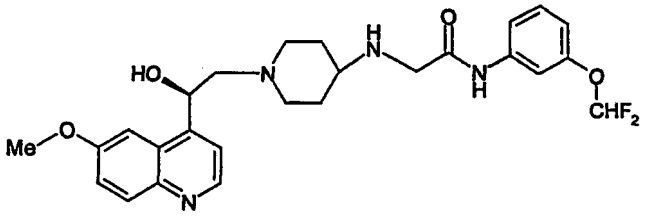
MS (+ve ion electrospray) m/z 467 (MH+)

Example 23. N-(3,5-Dichloro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



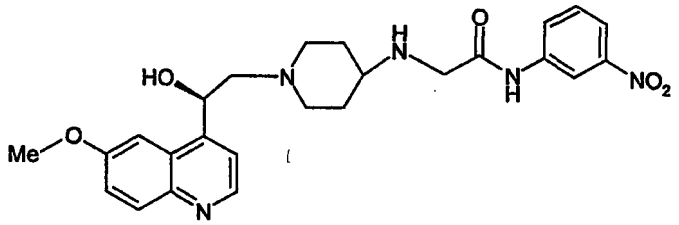
MS (+ve ion electrospray) m/z 503,505 (MH+)

Example 24. N-[2-(1,1-Difluoro-methoxy)-phenyl]-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



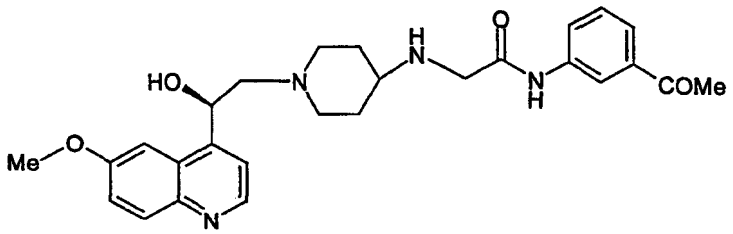
MS (+ve ion electrospray) m/z 501 (MH+)

Example 25. 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-(3-nitro-phenyl)-acetamide dioxalate



MS (+ve ion electrospray) m/z 480 (MH+)

Example 26. N-[3-Acetyl-phenyl]-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate

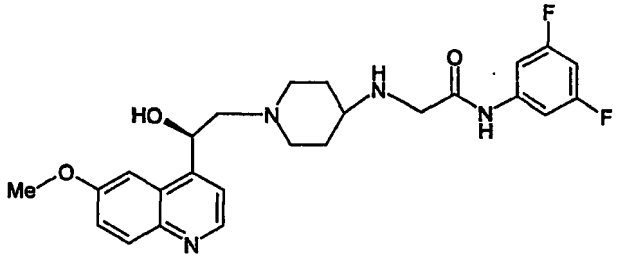


MS (+ve ion electrospray) m/z 477 (MH+)

Example 27. 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-(2-methoxycarbonyl-phenyl)-acetamide dioxalate
MS (+ve ion electrospray) m/z 493 (MH+)

Example 28. 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-N-(3-methoxycarbonyl-phenyl)-acetamide dioxalate
MS (+ve ion electrospray) m/z 493 (MH+)

Example 29. N-(3,5-Difluoro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



(a) 2-Bromo-N-(3,5-difluoro-phenyl)-acetamide

To a solution of 3,5-difluoroaniline (0.5g) in dichloromethane (10ml) at 0°C was added N,N-diisopropylethylamine (0.75ml) and bromoacetyl bromide (0.37ml), dropwise. The mixture was stirred for 3 hours and then quenched with sodium bicarbonate solution(20ml). Dichloromethane was added and the layers separated, the organic layer was evaporated and the residue chromatographed on silica gel (dichloromethane) to give a tan solid.

(b) Title compound

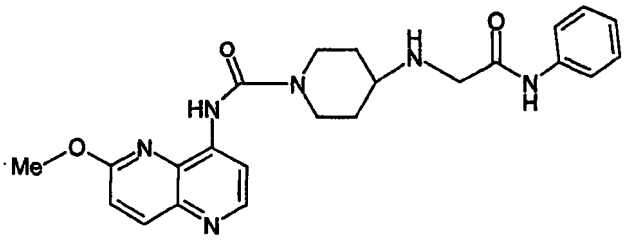
2-Bromo-N-(3,5-difluoro-phenyl)-acetamide (29a) (21.4mg) was dissolved in dimethylformamide (1ml). The amine (13c) (50mg) and potassium carbonate (25.2mg) were added and the mixture was stirred at room temperature for 3 hours and then the solvent was removed *in vacuo*. The residue was partitioned between dichloromethane (10ml) and water (10ml). The layers were separated and the aqueous layer was extracted with a further portion of dichloromethane (10ml). The combined extracts were evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a colourless oil (30mg).

MS (+ve ion electrospray) m/z 471 (MH+).

^{1}H NMR ($CDCl_3$) δ: 1.50 (2H, m), 1.98 (2H, brt), 2.25 (1H, brt), 2.41 (1H, brt), 2.55 (2H, brt), 2.85 (2H, dd), 3.30 (1H, brd), 3.40 (2H, s), 3.95 (3H, s), 5.45 (1H, m), 6.57 (1H, bt), 7.20 (3H, m) 7.45 (1H, dd), 7.62 (1H, d), 8.05 (1H, d), 8.78 (1H, d), 9.50 (1H, bs).

The oil was treated with oxalic acid in the usual way to give the dioxalate salt.

Example 30 4-(Phenylcarbamoylmethyl-amino)-piperidine-1-carboxylic acid (6-methoxy-[1,5]-naphthyridin-4-yl)-amide oxalate.



(a) 4-Hydroxy-6-methoxy-[1,5]-naphthyridine-3-carboxylic acid ethyl ester

3-Amino-6-methoxypyridine (12.41 g) and diethyl ethoxymethylene malonate (20.2 ml) in Dowtherm A (400 ml) were heated at reflux, under argon for 1 hour. The cooled reaction mixture was poured into pentane (1 litre). The precipitated solid was collected by filtration, washed with pentane and dried to afforded a solid (24.78 g, crude).
MS (+ve ion electrospray) m/z 249 (MH^+).

(b) 4-Hydroxy-6-methoxy-[1,5]-naphthyridine-3-carboxylic acid

The ester (30a) (0.642g) in 10% aqueous sodium hydroxide (115 ml) was heated at reflux for 1.5 hours. The reaction mixture was cooled then acidified with glacial acetic acid. The precipitated solid was collected by filtration, washed with water and dried *in vacuo* to afford a beige solid (0.542g).
MS (+ve ion electrospray) m/z 221 (MH^+).

(c) 4-Chloro-6-methoxy-[1,5]-naphthyridine

The acid (30b) (6.82 g) was heated in quinoline (20ml) at reflux for 2 hours, the mixture was cooled and poured into ether and the orange solid was filtered and washed with ether. A sample (3.87g) of the dried solid was treated with phosphorus oxychloride (30ml) at room temp for 3 hours, the solvent was removed *in vacuo* and the residue quenched with crushed ice (200g). The mixture was basified with ammonia solution and filtered. The solid was washed with dichloromethane (10 x 100ml), which was evaporated and chromatographed on silica gel (dichloromethane as eluent) to give a yellow solid (3.0g).
MS (+ve ion electrospray) m/z 195, 197 (MH^+).

(d) 4-Amino-6-methoxy-[1,5]-naphthyridine

A solution of the chloro compound (30c) (2.0g) in pyridine (30ml) was treated with n-propylamine hydrochloride (6.0g) and the mixture heated at reflux for 16 hours. The reaction mixture was cooled and partitioned between water and ethyl acetate. The aqueous phase was washed with ethyl acetate, the combined organics dried (Na_2SO_4) and the solvent removed under reduced pressure. Purification by chromatography on silica gel (methanol in dichloromethane) afforded a yellow solid (1.0g).

^{1}H NMR ($CDCl_3$) δ: 4.05 (3H, s), 5.36 (2H, bs), 6.71 (1H, d, J=5 Hz), 7.08 (1H, d), 8.10 (1H, d), 8.40 (1H, d).

MS (+ve ion electrospray) m/z: 176 (MH^+).

(e) 4-*tert*-Butoxycarbonylamino-1-(6-methoxy-[1,5]-naphthyridin-4-yl)aminocarbonylpiperidine

To a solution of 4-amino-6-methoxy-[1,5]-naphthyridine (30d) (2.1g,13.5 mmol) and 4-(dimethylamino)pyridine (1.62g) in anhydrous chloroform (45ml) was added N,N'-carbonyldiimidazole (3.28g, 20.1 mmol).The mixture was stirred for 4 hours at room temperature, then evporated and the residue was dissolved in anhydrous DMF (45ml). 4-*tert*-Butoxycarbonylaminopiperidine hydrochloride (3.34g, 13.5 mmol) and potassium carbonate (1.89g) were added, and the mixture was heated at 70°C overnight. The mixture was evaporated and the residue was mixed with water. The solid was filtered off and dried (3.89g).

MS (+ve ion electrospray) m/z 402 (MH+).

(f) 4-Amino-1-(6-methoxy-[1,5]-naphthyridin-4-yl)aminocarbonylpiperidine

The *tert*-butoxycarbonylamino compound (30e)(3.88g, 9.7 mmol) was treated with trifluoroacetic acid in dichloromethane and the solution was stirred at room temperature for 1.5 hours, then evaporated *in vacuo*. After addition of toluene and re-evaporation, the residue was treated with a 4M solution of hydrogen chloride in 1,4-dioxan (30ml). The resulting solid was triturated, filtered off and washed with ether. The crude hydrochloride was dissolved in water and washed twice with dichloromethane, basified to pH9 and evaporated to dryness. Extraction with 10% methanol-dichloromethane gave the free base (3.45g).

MS (+ve ion electrospray) m/z 302 (MH+).

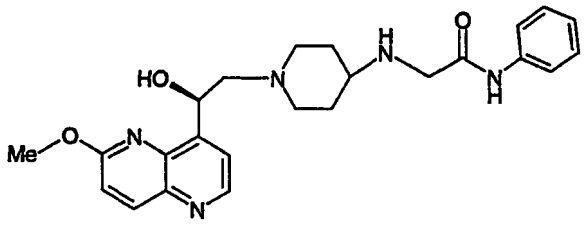
(g) Title compound

2-Bromo-N-phenyl-acetamide [prepared from aniline and bromoacetyl bromide by the method of Example (13a)] (71mg) was dissolved in dimethylformamide (2ml). The amine (30f) (100mg) and potassium carbonate (50mg) were added and the mixture was stirred at room temperature for 24 hours and then the solvent was removed *in vacuo*. The residue was partitioned between dichloromethane and water. The layers were separated and the aqueous layer was extracted with a further portion of dichloromethane. The combined extracts were evaporated and the residue chromatographed on silica gel (methanol-ethyl acetate) to give a colourless oil.

MS (+ve ion electrospray) m/z 435 (MH+).

The oil was treated with oxalic acid in the usual way to give the oxalate salt.

Example 31. 2-{1-[(R)-2-Hydroxy-2-(6-methoxy-[1,5]-naphthyridine-4-yl)-ethyl]-piperidin-4-ylamino}-N-phenyl-acetamide dioxalate



(a) 4-Hydroxy-6-methoxy-[1,5]-naphthyridine

5-Amino-2-methoxypyridine (55g, 0.44mol) in methanol (1000ml) with methyl propiolate (40ml, 0.44mol) was stirred for 48 hours, then evaporated and the product purified by chromatography on silica gel (dichloromethane) followed by recrystallisation from dichloromethane-hexane (44.6g, 48%).

The unsaturated ester (10.5g, 0.05mol) in warm Dowtherm A (50ml) was added over 3 minutes to refluxing Dowtherm A, and after a further 20 minutes at reflux the mixture was cooled and poured into ether. The precipate was filtered to give the title compound (6.26g, 70%)

(b) Bromomethyl-(6-methoxy-[1,5]-naphthyridin-4-yl)-ketone

The naphthyridine (31a) (10g, 0.057mol) in dichloromethane (200ml) containing 2,6-lutidine (9.94ml, 0.086mol) and 4-dimethylaminopyridine (0.07g, 0.0057mol) was cooled in ice and treated with trifluoromethanesulfonic anhydride (10.5ml, 0.063mol). After stirring for 2.5 hours the mixture was washed with saturated ammonium chloride solution, dried, evaporated and purified on silica (dichloromethane). The triflate (13.2g, 0.044mol) in DMF (200ml) with triethylamine (12ml, 0.086mol) butyl vinyl ether (22ml, 0.17mol), palladium (II) acetate (0.97g, 0.0044mol) and 1,3-bis(diphenylphosphino)propane (1.77g, 0.0044mol) was heated at 60°C for 3 hours then evaporated and chromatographed on silica gel (dichloromethane) to give a yellow solid (10.7g, 95%). This was dissolved in THF (250ml), water (40ml) and treated with N-bromosuccinimide (7.4g, 0.042 mol) for 1 hour, then evaporated and chromatographed on silica gel (dichloromethane) to give the ketone (10.42g, 98%).

(c) [R]-2-Bromo-1-(6-methoxy-[1,5]-naphthyridin-4-yl)ethanol

The ketone (31b) (6.6g, 0.023mol) in toluene was treated with (+)-DIP-chloride (12g, 0.037mol) and stirred overnight, then diethanolamine (15g, 0.14mol) added and the mixture stirred for 3 hours, filtered and evaporated. Chromatography on silica gel (ethyl acetate-hexane)gave a white solid (4.73g, 73%).

(d) [R]-2-(6-methoxy-[1,5]-naphthyridin-4-yl)oxirane

The alcohol (31c) (4.8g, 0.017mol) in methanol (20ml) was stirred with potassium carbonate (2.6g, 0.019 mol) for 1 hour, then evaporated and chromatographed on silica

gel (ethyl acetate-hexane-dichloromethane) to give a solid (3.14g, 92%), (91% ee by chiral HPLC).
MS (+ve ion electrospray) m/z 203 (MH+).
(e) 4-*tert*-Butoxycarbonylamino-1-[2-(R)-hydroxy-2-(6-methoxy-[1,5]-naphthyridin-4-yl)]ethylpiperidine.

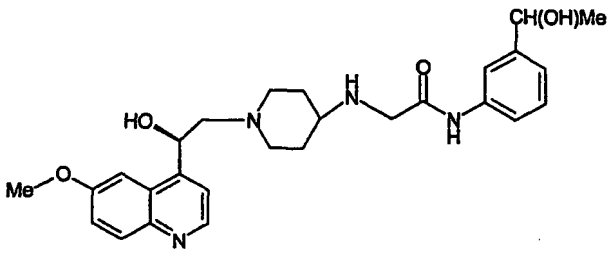
This was prepared from [R]-2-(6-methoxy-[1,5]-naphthyridin -4-yl)oxirane (31d) (3.0g, 14.9mmol) by the method of Example (13b), to give a foam (5.34g).
MS (+ve ion electrospray) m/z 403 (MH+).
(f) 4-Amino-1-[2-(R)-hydroxy-2-(6-methoxy-[1,5]-naphthyridin-4-yl)]ethylpiperidine.

This was prepared from the *tert*-butoxycarbonylamino compound (31e) (5.15g) by the method of Example (13c), to give a solid (3.15g).
MS (+ve ion electrospray) m/z 303 (MH+).
(g) Title compound

This was prepared from the amine (31f) (0.1g) and 2-bromo-N-phenyl-acetamide (0.071g) by the method of Example (30g) to give the free base of the title compound (0.020g).
^{1}H NMR ($CDCl_3$) δ: 1.45–2.65 (9H, m), 2.85 (1H, m), 3.05 (1H, dd), 3.30 (1H, m), 3.45 (2H, s), 3.95 (3H, s), 5.70 (1H, m) 7.10 (2H, m), 7.35 (2H, t), 7.65 (2H, d), 7.78 (1H, m), 8.20 (1H, d), 8.78 (1H, d), 9.40 (1H, bs).
MS (+ve ion electrospray) m/z 436 (MH+).

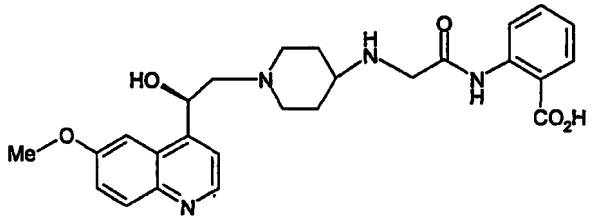
This was converted to the dioxalate salt (0.027g) in the usual way

Example 32. N-[3-(1-Hydroxy-ethyl)-phenyl]-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



The ketone Example (26) (23 mg, 0.05 mmol) was dissolved in methanol (1ml) and sodium borohydride (1.8mg, 0.05 mmol) was added. The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated and the residue partitioned between dichloromethane (5ml) and sodium bicarbonate solution (5ml). The organic layer was dried ($MgSO_4$), filtered and evaporated to give a colourless oil (23mg).
MS (+ve ion electrospray) m/z 479 (MH+)
The dioxalate salt was prepared in the usual manner.

Example 33. N-[2-Carboxy-phenyl]-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate

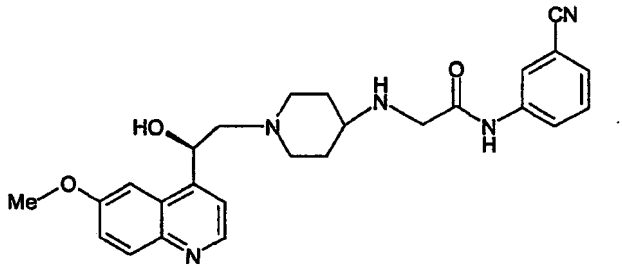


The ester Example (27) (36mg, 0.07 mmol) was dissolved in tetrahydrofuran (1ml) and 2M sodium hydroxide solution (1ml, 0.2 mmol) followed by water (0.5ml) were added. The mixture was heated at 60°C for 1 hour, cooled to room temperature and 5M hydrochloric acid added until the solution was pH 4. The mixture was evaporated to dryness and methanol (5ml) was added. The methanolic solution was filtered to give a solid, in quantitative yield.

MS (+ve ion electrospray) m/z 479 (MH+)

The dioxalate salt was prepared in the usual manner.

Example 34. N-[3-Cyano-phenyl]-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



(a) (1-Benzyl-piperidin-4-ylamino)-acetic acid benzyl ester

1-Benzyl-4-piperidone (23.5g, 124 mmol) and glycine benzyl ester (124 mmol) were stirred in dichloromethane (500ml) with 3A molecular sieves at 0°C for 1 hour and sodium triacetoxyborohydride (18.2g) was added portionwise over 15 minutes, and the mixture was stirred at room temperature for 1.5 hours. The mixture was cooled to 0°C and sodium bicarbonate solution was added, and the organic layer was separated, dried, evaporated and chromatographed on silica gel (ammonia-methanol-ethyl acetate) to afford an oil (29.21g).

(b) [(1-Benzyl-piperidin-4-yl)-*tert*-butoxycarbonyl-amino]-acetic acid benzyl ester

The amine (34a) (29.21g) in dichloromethane (200ml) was treated with di-*tert*-butyl dicarbonate (20.66g) and 4-dimethylaminopyridine (0.10g) and the solution was

stirred at room temperature for 2 hours, evaporated and chromatographed on silica gel (ethyl acetate-dichloromethaane) to afford an oil (28.1g).

(c) 4-[(Benzyloxycarbonylmethyl)-(*tert*-butoxycarbonyl)-amino]-piperidine-1-carboxylic acid 1-chloro-ethyl ester

The piperidine (34b) (5.15g) in dichloromethane (50ml) at 0°C was treated with di-isopropylethylamine (1.8g) and 1-chloroethyl chloroformate (1.4ml) for 1 hour, evaporated, and chromatographed on silica gel (ethyl acetate-dichloromethaane) to afford an oil (4.3g).

(d) (*tert*-Butoxycarbonyl-piperidin-4-yl-amino)-acetic acid benzyl ester

The carbamate (34c) (11.9g) in methanol (100ml) was left at room temperature for 4 days, evaporated, and partitioned between ethyl acetate and sodium bicarbonate solution. The organic fraction was dried, evaporated, and chromatographed on silica gel to afford an oil (1.2g).

(e) ((*tert*-Butoxycarbonyl)-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl}-amino)-acetic acid benzyl ester

The piperidine (34d) (500mg, 1.44 mmol) in acetonitrile (5ml) under argon at room temperature was treated with [R]-2-(6-methoxyquinolin-4-yl)oxirane (1a) (290mg, 1.44 mmol) and lithium perchlorate (153mg, 1.44 mmol). The mixture was stirred at this temperature for 96 hours then the solvent was evaporated and the residue partitioned between dichloromethane and sodium bicarbonate solution. The layers were separated and the aqueous portion was extracted with dichloromethane. The combined organic layers were evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a colourless oil (529mg, 67%).

(f) ((*tert*-Butoxycarbonyl)-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl}-amino)-acetic acid

The ester (34e) (520mg, 0.93 mmol) was dissolved in ethanol (50ml) and 10% palladium on charcoal (0.5g) was added. The mixture was hydrogenated for 4 hours, then filtered and evaporated. The colourless solid (427mg) obtained was used crude in the next step.

MS (+ve ion electrospray) m/z 460 (MH+)

(g) ((*tert*-Butoxycarbonyl)-N-[3-cyano-phenyl]-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl-amino)-acetamide

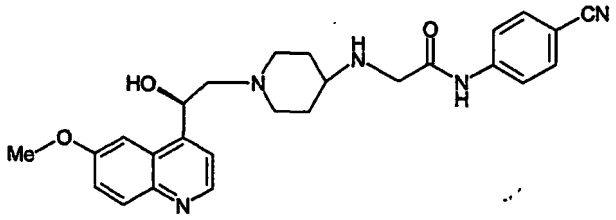
The acid (34f) (100mg, 0.22 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (42mg, 0.22 mmol) were stirred at room temperature in dichloromethane for 10 minutes. 3-Cyanoaniline (26mg, 0.22 mmol) was added and the mixture stirred at room temperature for 12 hours. Dichloromethane and water were added and the layers separated. The aqueous phase was washed with dichloromethane and the

combined organics were evaporated and the residue chromatographed on silica gel, (methanol-dichloromethane) to give a colorless oil (42mg, 34%).
MS (+ve ion electrospray) m/z 560 (MH+)
(h) Title compond

The piperidine (34g) (42mg, 0.07 mmol) was treated with dichloromethane (3ml) and trifluorofluoroacetic acid (1ml) for 1 hour. The solvents were evaporated and the residue treated with oxalic acid in the usual manner to give the dioxalate (43 mg).
MS (+ve ion electrospray) m/z 460 (MH+)

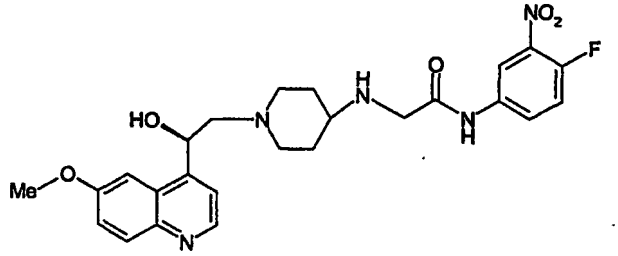
The following Examples 35-36 were prepared by the Method of Example 34:

Example 35. N-[4-Cyano-phenyl]-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



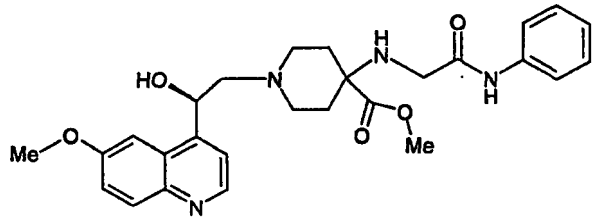
MS (+ve ion electrospray) m/z 460 (MH+)

Example 36. N-[4-Fluoro-3-nitro-phenyl]-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino)-acetamide dioxalate



MS (+ve ion electrospray) m/z 498 (MH+)

Example 37 2-{1-[2-(R)-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-4-methoxycarbonyl-piperidin-4-ylamino}-N-phenyl-acetamide dioxalate



(a) Methyl 4-benzyloxycarbonylamino-1-*tert*-butoxycarbonylpiperidine-4-carboxylate.

4-Amino-1-*tert*-butoxycarbonylpiperidine-4-carboxylic acid (18.0g) was dissolved in 0.03M aqueous sodium hydroxide (750ml), and 1,2-dimethoxyethanol (DME, 100ml). The pH was adjusted to 9.5 with dilute hydrochloric acid, and the suspension was added to an ice-cold solution of N-(benzyloxycarbonyloxy)succinimide (28.8g) in DME (100ml). The pH was kept at 9.5 by addition of aqueous sodium hydroxide, and the mixture was stirred at room temperature. More N-(benzyloxycarbonyloxy)succinimide (3g) was added after 7 hours, then stirring was continued overnight. After evaporation, the aqueous residue was extracted with ether then acidified to pH4 and extracted with ethyl acetate. This extract was washed with dilute hydrochloric acid, water and brine, dried and evaporated. Trituration of the oily residue gave 4-benzyloxycarbonylamino-1-*tert*-butoxycarbonylpiperidine-4-carboxylic acid (23g). This acid (23g) was esterified by treatment with methyl iodide (3.8ml), and potassium carbonate (16.6g) in acetone (200ml) at room temperature for 3 days. Filtration, evaporation, partitioning of the residue between dichloromethane and water and evaporation of the organic phase gave the methyl ester (21.05g).

MS (+ve ion electrospray) m/z 293 (MH^+- *t*-BOC)

(b) Methyl amino-1-*tert*-butoxycarbonylpiperidine-4-carboxylate

The piperidine (37a) (12.77g) was treated with ethanol (100ml) and 10% palladium on charcoal (2g). The mixture was hydrogenated for 72 hours, filtered and evaporated to give a colourless oil (5.66g, 65%).

(c) [1-*tert*-Butoxycarbonyl-4-methoxycarbonyl-piperidin-4-ylamino]-N-phenyl-acetamide

The amine (37b) (3.57g, 12.6 mmol) was dissolved in dimethylformamide (20ml). Potassium carbonate (1.79g, 13 mmol) and N-phenyl bromoacetamide (2.8g, 13 mmol) were added and the mixture was stirred at room temperature for 24 hours and then the solvent removed *in vacuo*. The residue was partitioned between dichloromethane and water. The layers were separated and the aqueous layer was extracted with a further portion of dichloromethane. The combined extracts were evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a colourless oil (4.35g, 93%).

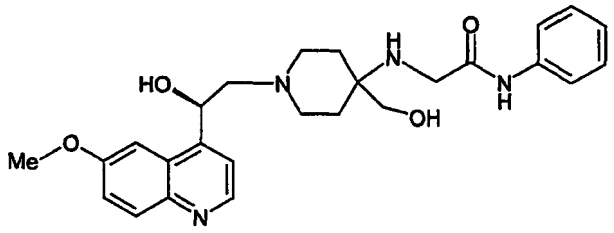
MS (+ve ion electrospray) m/z 392 (MH+)

(d) [4-Methoxycarbonyl-piperidin-4-ylamino]-N-phenyl-acetamide

The piperidine (37c) (4.35g, 11.7 mmol) was treated with dichloromethane (20ml) and trifluorofluoroacetic acid (10ml) for 1 hour. The solvents were evaporated and the residue treated with sodium bicarbonate solution. The aqueous mixture was extracted with dichloromethane (100ml) which contained impure product (1.5g, discarded). The aqueous layer was treated with 2M sodium hydroxide solution until pH 11 and then

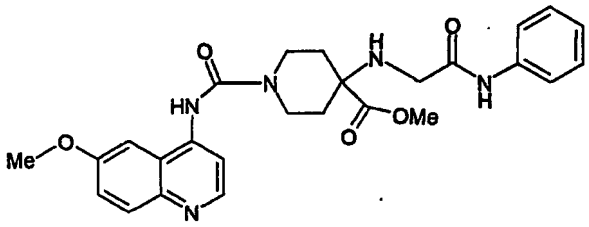
extracted with dichloromethane (5 x 100 ml). The combined organic extracts were evaporated to give a colourless oil (1.86g, 55%).
MS (+ve ion electrospray) m/z 292 (MH+)
(e) Title compound
The piperidine (37d) (286mg, 1 mmol) in acetonitrile (2ml) under argon at room temperature was treated with [R]-2-(6-methoxyquinolin-4-yl)oxirane (1a) (201mg, 1 mmol) and lithium perchlorate (106.4mg, 1 mmol). The mixture was stirred at this temperature for 20 hours then the solvent was evaporated and the residue partitioned between dichloromethane and sodium bicarbonate solution. The layers were separated and the aqueous portion was extracted with dichloromethane. The combined organic layers were evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a colourless oil (258mg, 52%).
MS (+ve ion electrospray) m/z 493 (MH+)
A portion was treated with oxalic acid to produce the dioxalate salt in the usual manner.

Example 38 2-{1-[2-(R)-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-4-hydroxymethyl-piperidin-4-ylamino}-N-phenyl-acetamide dioxalate



The ester Example (37) (109mg, 0.22 mmol) was dissolved in tetrahydrofuran (2ml) under argon and cooled to 0°C. A 1M solution of lithium aluminium hydride in tetrahydrofuran (0.22ml, 0.22 mmol) was added and the mixture stirred for 1 hour. 2M Sodium hydroxide solution (10ml) was added carefully followed by dichloromethane (15ml). The layers were separated and the aqueous layer was extracted with dichloromethane, the combined organics were evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a colourless oil (34mg, 31%)
MS (+ve ion electrospray) m/z 465 (MH+)
^{1}H NMR ($CDCl_3$) δ: 1.70 (4H, m), 2.55 (3H, m), 2.85 (3H, m), 3.35 (2H, s), 3.50 (2H, s), 3.85 (3H, s), 5.45 (1H, dd), 7.15 (1H, d), 7.35 (3H, m), 7.40 (1H, dd), 7.60 (2H, d), 7.65 (1H, d), 8.05 (1H, d), 8.75 (1H, d), 9.30 (1H, brs).
It was treated with oxalic acid to produce the dioxalate salt in the usual manner.

Example 39 4-Methoxycarbonyl-4-(phenylcarbamoylmethyl-amino)-piperidine-1-carboxylic acid (6-methoxy-quinolin-4-yl)-amide oxalate.

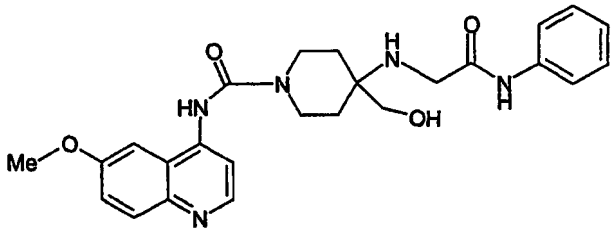


The piperidine (37d) (291mg, 1 mmol) was heated in dimethylformamide (2ml) with 4-(1-imidazolylcarbonyl)amino-6-methoxyquinoline (5b) (268mg, 1 mmol) at 70°C for 12 hours. The solvent was evaporated and the residue partitioned between dichloromethane and sodium bicarbonate solution. The layers were separated and the aqueous portion was extracted with dichloromethane. The combined organic layers were evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a colourless oil (154mg, 31%)

MS (+ve ion electrospray) m/z 492 (MH+)

It was treated with oxalic acid to produce the oxalate salt in the usual manner.

Example 40 4-Hydroxymethyl-4-(phenylcarbamoylmethyl-amino)-piperidine-1-carboxylic acid (6-methoxy-quinolin-4-yl)-amide oxalate.

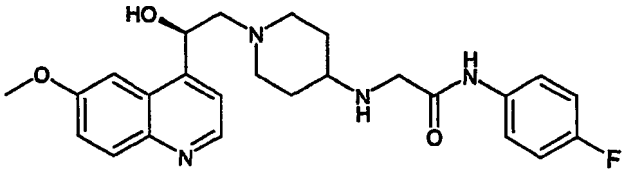


The ester Example 39 (140mg, 0.28 mmol) was dissolved in tetrahydrofuran (2ml) under argon and cooled to 0°C. A 1M solution of lithium aluminium hydride (0.14ml, 0.14 mmol) was added and the mixture stirred for 10 minutes. Further lithium aluminium hydride (0.14ml) was added and the mixture stirred for 1 hour. 2M sodium hydroxide solution was added carefully followed by dichloromethane. The layers were separated and the aqueous layer was extracted with dichloromethane, the combined organics were evaporated and the residue chromatographed on silica gel (methanol-dichloromethane) to give a colourless oil (57mg, 44%).

MS (+ve ion electrospray) m/z 464 (MH+)

It was treated with oxalic acid to produce the oxalate salt in the usual manner.

Example 41. N-(4-Fluoro-phenyl)-2-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-acetamide dioxalate



(a) {1-[(R)-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-acetic acid benzyl ester

A solution of ketone (1c) (0.5g) and benzyl glycinate (0.37g) in dichloromethane (5ml) was treated with sodium triacetoxyborohydride (0.47g). After 16 hours the mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The dichloromethane extract was dried and evaporated to give a yellow solid. Chromatography on silica gel (methanol-dichloromethane) afforded the product as a white solid (0.27g)

MS (+ve ion electrospray) m/z 450 (MH+)

(b) (*tert*-Butoxycarbonyl-{1-[(R)-2-*tert*-butoxycarbonyloxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl}-amino)-acetic acid benzyl ester

A solution of (41a) (0.27g) in chloroform (5ml) was treated with di-*tert*-butyl dicarbonate (0.4g) and 4-N,N-dimethylaminopyridine (40mg).for 16 hours The product was chromatography on silica gel (methanol/ethyl acetate) to afford an oil (0.16g)

MS (+ve ion electrospray) m/z 650 (MH+)

(c) (*tert*-Butoxycarbonyl-{1-[(R)-2-*tert*-butoxycarbonyloxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl}-amino)-acetic acid

A solution of (41b) (0.16g) in ethanol (15ml) was hydrogenated over 10% palladium on charcol (0.2g) for 2 hours. Filtration and evaporation gave a mixture of (49c) and (*tert*-butoxycarbonyl-{1-[2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl}-amino)-acetic acid as an oil (0.12g)

MS (+ve ion electrospray) m/z 560 (MH+) (41c)

MS (+ve ion electrospray) m/z 444 (MH+) (by-product)

(d) Carbonic acid (R)-2-(4-{*tert*-butoxycarbonyl-[(4-fluoro-phenylcarbamoyl)-methyl]-amino}-piperidin-1-yl)-1-(6-methoxy-quinolin-4-yl)-ethyl ester *tert*-butyl ester

A solution of (41c) (0.12g) in N,N-dimethylformamide (2ml) was treated with 4-fluoroaniline (30mg) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (50mg). After 16 hours the mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The ethyl acetate extract was dried and evaporated to give a yellow oil. Chromatography on silica gel (methanol-ethyl acetate) afforded (41d) as an oil (40mg).

The earlier fractions from the column gave [(4-fluoro-phenylcarbamoyl)-methyl]-{1-[2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester as an oil (17mg).

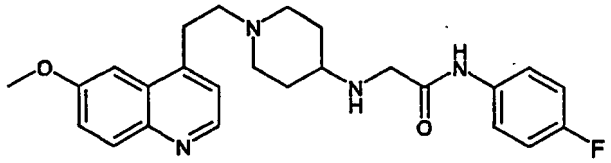
(e) Title compound

A solution of (41d) (40mg) in trifluoroacetic acid (5ml) was stirred for 2.5 hours then evaporated to dryness. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The ethyl acetate extract was dried and evaporated to give a yellow oil. Chromatography on silica gel (methanol-ethyl acetate) afforded the title compound as an oil (20mg).

MS (+ve ion electrospray) m/z 453 (MH+).

This was converted to the dioxalate salt in the usual way.

Example 42. N-(4-Fluoro-phenyl)-2-{1-[2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-acetamide dioxalate

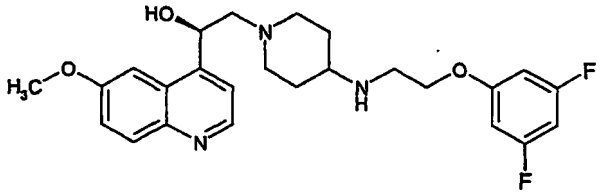


A solution of [(4-fluoro-phenylcarbamoyl)-methyl]-{1-[2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester (17mg) (see earlier fraction in (41d) above) in trifluoroacetic acid (3ml) was stirred for 1 hour then evaporated to dryness. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The ethyl acetate extract was dried and evaporated to give a yellow oil. Chromatography on silica gel (methanol-ethyl acetate) afforded the title compound as an oil (9mg).

MS (+ve ion electrospray) m/z 437 (MH+).

This was converted to the dioxalate salt in the usual way.

Example 43. 4-[2-(3,5-Difluorophenoxy)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



(a) (3,5-Difluorophenoxy)-acetaldehyde

A solution of bromoacetaldehyde dimethyl acetal (1g) and 3,5-difluorophenol (0.8g) was treated with potassium carbonate (0.8g) and heated at 100 °C for 24hours. The

mixture was partitioned between ether and 2N aqueous sodium hydroxide solution. The ether extract was dried and evaporated to afford 1-(2,2-dimethoxyethoxy)-3,5-difluorobenzene as an oil (0.2g) This was dissolved in a 2% solution of water in tetrahydrofuran (5 ml), treated with acidic Amberlyst-15 resin (0.75g) and heated at 60°C for 10 hours. The mixture was filtered and evaporated affording the title aldehyde as an oil (0.1g).

MS (+ve ion electrospray) m/z 173 (MH+)

(b) Title compound

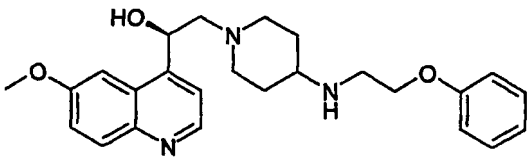
A mixture of aldehyde (43a) (0.1g) and amine (13c) (0.09g) in dichloromethane-methanol (2 ml/0.2 ml) was treated with 3A molecular sieves (0.2g) then after 0.5 hours with sodium triacetoxyborohydride (0.2g). After 16 hours the mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The dichloromethane extract was dried and evaporated to give a yellow solid. Chromatography on silica gel (methanol-dichloromethane) afforded the product as a white solid (0.075g, 55%).

^{1}H NMR ($CDCl_3$) δ: 1.60 (2H, m), 2.00 (2H, m), 2.25 (1H, m),) 2.50 (3H, m), 2.80 (2H, m), 3.00 (2H, t), 3.25 (1H, m), 3.90 (3H, m), 4.05 (2H, m), 5.45 (1H, dd), 6.45 (3H, m), 7.20 (1H, d), 7.35 (1H, dd), 7.65 (1H, d), 8.05 (1H, d), 8.80 (1H, d)

MS (+ve ion electrospray) m/z 458 (MH+)

This was converted to the dioxalate salt by treating a deuterochloroform solution with a solution of oxalic acid (36mg) in ether. The precipitate was isolated by centrifugation, resuspended in ether and again isolated by centrifugation. Drying *in vacuo* afforded the title compound as a white solid (66mg).

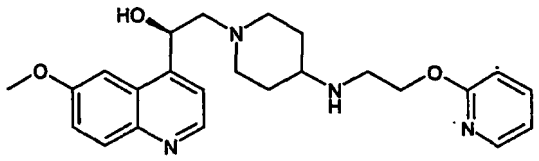
Example 44. 4-(2-Phenoxyethyl)amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



A solution of the ketone (1c) (1.0g) and 2-phenoxyethylamine (0.5g) in dichloromethane was treated with 3A molecular sieves (0.5g) and shaken for 1 hour. Sodium triacetoxyborohydride (1.0g) was added and the mixture shaken for 24 hours. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The dichloromethane extract was dried and evaporated to give a yellow oil. Chromatography on silica eluting with a methanol/dichloromethane gradient

afforded the product as an oil (0.97g). This was converted to the dioxalate salt (0.9g) by the same procedure as for Example (43).
MS (+ve ion electrospray) m/z 422 (MH+)
^{1}H NMR ($CDCl_3$) δ: 1.60 (2H, m), 2.00 (2H, m), 2.05 (1H, m), 2.50 (3H, m), 2.80 (2H, m), 3.02 (2H, t), 3.25 (1H, m), 3.90 (3H, m), 4.08 (2H, m), 5.50 (1H, dd), 6.95 (3H, m), 7.20 (1H, d), 7.30 (2H,m), 7.35 (1H, dd), 7.65 (1H, d), 8.05 (1H, d), 8.80 (1H, d)

Example 45. 4-[2-(Pyridin-2-yloxy)-ethylamino]-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

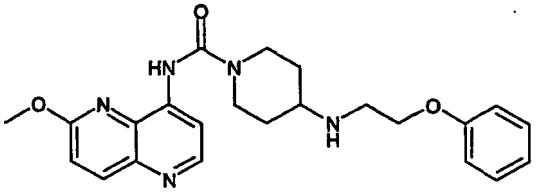


(a) 2-(Pyridin-2-yloxy)-ethylamine

This was prepared in 71% yield from 2-chloropyridine and ethanolamine according to the procedure of G. Tarrago *et al*, Tetrahedron, 1988, **44**, 91.
MS (+ve ion electrospray) m/z 139 (MH+)
(b) Title compound

This was prepared by reductive alkylation with amine (45a) (70 mg) and ketone (1c) (0.15g) according to the same procedure as for Example (44), giving the title compound (free base) as a white foam (95 mg, 45%), which was converted to the dioxalate salt (120 mg) by the same procedure as for Example 43.
^{1}H NMR ($CDCl_3$) δ: 1.60 (2H, m), 1.95 (2H, m), 2.15 (1H, m), 2.50 (3H, m), 2.80 (2H, m), 3.08 (2H, t), 3.25 (1H, m), 3.90 (3H, m), 4.45 (2H, t), 5.45 (1H, dd), 6.78 (1H, d), 6.90 (1H, t), 7.25 (1H, d), 7.40 (1H, dd), 7.55 (1H, m), 7.65 (1H, d), 8.05 (1H, d), 8.20 (1H, m), 8.80 (1H, m).
MS (+ve ion electrospray) m/z 423 (MH+)

Example 46. 4-(2-Phenoxyethylamino)-1-(6-methoxy-[1,5]-naphthyridin-4-yl)aminocarbonylpiperidine oxalate



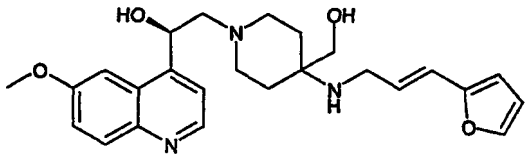
A solution of amine (30f) (0.1g) and phenoxyacetaldehyde (0.16g) in dichloromethane and methanol (1ml) was stirred for 0.5 hours, then sodium triacetoxyborohydride (0.11g) was added. After 6 hours the mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The dichloromethane extract was dried and evaporated to give a yellow oil. Chromatography on silica (methanol-dichloromethane) afforded the free base of the title compound as a solid (0.025g). This was converted to the oxalate salt (0.024g) by the same procedure as for Example (44).

^{1}H NMR ($CDCl_3$) δ: 1.50 (2H, m), 2.00 (2H, m), 2.85 (1H, m), 3.05 (2H, t), 4.10 (7H, m), 6.95 (3H, m), 7.15 (1H, d), 7.30 (2H, m), 8.20 (1h, d), 8.30 (1H, d), 8.65 (1H, d), 9.10 (1H, bs).

MS (+ve ion electrospray) m/z 422 (MH+).

This was converted to the oxalate salt (0.024g) by the same procedure as for Example 44.

Example 47. 4-[*trans*-1-(2-Furyl)-3-propenyl]amino-4-hydroxymethyl-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



(a) Allyl 4-benzyloxycarbonylaminopiperidine-4-carboxylate.

The acid intermediate described in Example 37a (9.62g) was esterified by treatment with allyl bromide (2.2ml), potassium carbonate (7.04g) and potassium iodide (catalytic) in acetone (100ml) under reflux for 20 hours. Evaporation, partitioning of the residue between dichloromethane and water and evaporation of the organic phase gave the allyl ester (10.2g). This was then treated with trifluoroacetic acid in dichloromethane for 1.5 hours at room temperature to give, after basification of the triflate salt and extraction with dichloromethane-methanol, the free base (6.58g).

(b) 4-Benzyloxycarbonylamino-1-[(R)-2-hydroxy-2-(6-methoxyquinolin-4-yl)-ethyl]-piperidine-4-carboxylic acid, allyl ester

A solution of piperidine (47a) (1.85g, 5.8 mmol) and oxirane (1a) (1.2g, 5.8 mmol) in acetonitrile (10ml) was treated with lithium perchlorate (0.62g, 5.8 mmol) and stirred at room temperature for 20 hours. The mixture was evaporated and the residue partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The dichloromethane extract was dried and evaporated to give an oil. Chromatography on silica gel (methanol-dichloromethane) afforded the product as an oil (1.6g).

MS (+ve ion electrospray) m/z 520 (MH+).

(c) 4-Amino-1-[(R)-2-hydroxy-2-(6-methoxyquinolin-4-yl)-ethyl]-piperidine-4-carboxylic acid, propyl ester

A solution of (47b) (1.58g) in ethanol (100ml) was hydrogenated over 10% palladium on charcol (0.1g) for 16 hours. Filtration, evaporation, and chromatography on silica gel (methanol/dichloromethane) afforded the product as an oil (0.53g).
MS (+ve ion electrospray) m/z 388 (MH+).

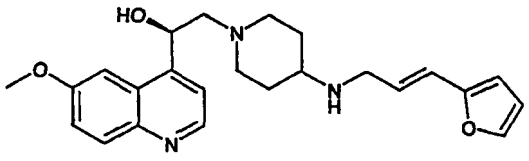
(d) (R)-2-(4-Amino-4-hydroxymethylpiperidin-1-yl)-1-(6-methoxyquinolin-4-yl)-ethanol

A solution of ester (47c) (0.52 g, 1.3 mmol) in tetrahydrofuran (8ml) was treated at 0°C with a solution of lithium aluminium hydride in tetrahydrofuran (1M; 1.4ml, 1.4 mmol). After 1 hour aqueous sodium hydroxide (2M, 20ml) was added and the mixture was extracted with dichloromethane (30ml). Drying, evaporation, and chromatography on silica gel (methanol-dichloromethane) afforded the product as an oil (0.24g).
MS (+ve ion electrospray) m/z 332 (MH+).

(e) Title compound

A solution of the amine (47d) (0.14g) and *trans*-(2-furyl)-propenal (0.06g) in dichloromethane (5ml) was treated with sodium triacetoxyborohydride (0.1g). After 16 hours, methanol (1ml) was added followed by sodium borohydride (50mg). After 0.25 hours the mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The dichloromethane extract was dried and evaporated to give an oil. Chromatography on silica (methanol-dichloromethane) afforded an oil (45 mg) which was converted to the dioxalate salt (58 mg) by the procedure of Example (43).
^{1}H NMR ($CDCl_3$) δ: 1.80 (4H, m), 2.70 (2H, m), 2.90 (2H, m), 3.30 (2H, d), 3.50 (2H, s), 3.95 (3H, s), 4.05 (2H, m), 5.55 (1H, dd), 6.15-6.25 (2H, m), 6.35-6.50 (2H, m), 7.18 (1H, d), 7.30-7.40 (2H, m), 7.65 (1H, d), 8.05 (1H, d), 8.78 (1H, d)
MS (+ve ion electrospray) m/z 462 (MH+).

Example 48. 4-[*trans*-1-(2-Furyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



The aminopiperidine (13c) (0.60g,1.99 mmol) and *trans*-3-(2-furyl)propenal (0.24g) were heated under reflux in chloroform (10ml) over magnesium sulphate (2.5g) for 19 hours. After filtation and evaporation of solvent, the residue was dissolved in methanol (10ml), cooled in ice and sodium borohydride (90 mg) was added. After 4 hours stirring at room temperature, the mixture was evaporated and the residue was dissolved in

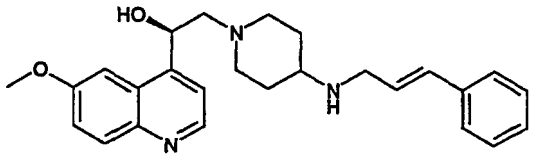
water and extracted with dichloromethane. The extract was dried and evaporated and the residue was chromatographed on silica gel (methanol-dichloromethane) to give an oil (0.63g).

^{1}H NMR ($CDCl_3$): δ 1.50 (2H, m), 1.97 (2H, broad t), 2.22 (1H, td), 2.37-2.67 (3H, m), 2.82 (2H, m), 3.26 (1H, m), 3.43 (2H, d), 3.93 (3H, s), 5.43 (1H, dd), 6.21 (1H, d), 6.26 (1H, t), 6.35 (1H, m), 6.39 (1H, d), 7.18 (1H, d), 7.34 (1H, s), 7.36 (1H, dd), 7.64 (1H, d), 8.03 (1H, d), 8.77 (1H, d).

MS (+ve ion electrospray) m/z 408 (MH+).

The free base (102mg) in dichloromethane was treated with 0.1 M oxalic acid in ether (5ml) to give the dioxalate salt (126mg).

Example 49. 4-[trans-1-Phenyl-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



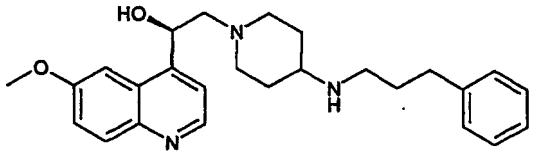
This was prepared from amine (13c) and cinnamaldehyde according to the same procedure as Example (43) affording an oil (11 mg, 15%).

^{1}H NMR ($CDCl_3$) δ: 1.50 (2H, m), 2.00 (2H, m), 2.20-2.60 (4H, m), 2.80 (2H, m), 3.25 (1H, m), 3.45 (2H, d), 3.95 (3H, s), 5.40 (1H, dd), 6.30 (1H, dt), 6.50 (1H, d), 7.20-7.40 (7H, m), 7.65 (1H, d), 8.05 (1H, d), 8.75 (1H, d).

MS (+ve ion electrospray) m/z 418 (MH+)

This was converted to the dioxalate (14 mg) by the same procedure as Example (1).

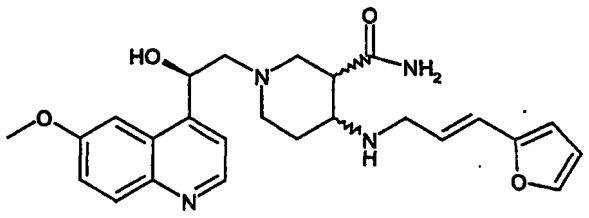
Example 50. 4-[-3-Phenylpropyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



This was prepared from amine (13c) and 3-phenylpropionaldehyde according to the same procedure as Example (43) affording an oil (19mg, 14%), which was converted to the dioxalate salt (18mg) by the same procedure as Example (1).

^{1}H NMR ($CDCl_3$) δ: 1.50 (2H, m), 1.80-2.00 (4H, m), 2.20 (1H, t), 2.40 (1H, t), 2.55 (2H, m), 2.65 (4H, m), 2.85 (2H, m), 3.25 (1H, m), 3.90 (3H, s), 5.40 (1H, dd), 7.15 (3H, m), 7.25 (3H, m), 7.35 (1H, dd), 7.65 (1H, d), 8.00 (1H, d), 8.80 (1H, d).
MS (+ve ion electrospray) m/z 420 (MH+)

Example 51. *cis*-3-(R/S)-Aminocarbonyl-4-(S/R)-[*trans*-1-(2-furyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



(a) *cis*-1-*tert*-Butoxycarbonyl-3-(R/S)-ethoxycarbonyl-4-(S/R)- [*trans*-1-(2-furyl)-3-propenyl]amino piperidine.

The aminopiperidine(2c) (1.20g) was reductively alkyated with *trans*-3-(2-furyl)propenal (0.54g) by the method of Example (48). The crude product was chromatographed on silica gel (methanol-dichloromethane) to give the [*trans*-1-(2-furyl)-3-propenyl]amino compound (1.06g).
MS (+ve ion electrospray) m/z 379 (MH+).
(b) *cis*-3-(R/S)-Ethoxycarbonyl-4-(S/R)-[*trans*-1-(2-furyl)-3-propenyl]amino piperidine.

The 1-*tert*-butoxycarbonylpiperidine (51a) (1.06g) was treated with trifluoroacetic acid (5ml) and 1,3-dimethoxybenzene (3.12ml) in dichloromethane (l). After 1.5 hours at room temperature, the mixture was evaporated and the residue was triturated with ether, dissolved in aqueous sodium bicarbonate and extracted with dichloromethane. The extracts were dried and evaporated, and the crude product was chromatographed on silica gel (methanol-dichloromethane) to give the piperidine (0.34g).
MS (+ve ion electrospray) m/z 279 (MH+).
(c) *cis*-3-(R/S)-Ethoxycarbonyl-4-(S/R)-[*trans*-1-(2-furyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine

The piperidine (51b) (0.17g), [R]-2-(6-methoxyquinolin-4-yl)oxirane (1a) (0.12g) and lithium perchlorate (64mg) were stirred in acetonitrile (1ml) at room temp. for 3 days. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with water and brine, dried and evaporated. The crude product was chromatographed on silica gel (methanol-dichloromethane) to give the hydroxyethylpiperidine (0.16g).
MS (+ve ion electrospray) m/z 480 (MH+)
(d) Title compound.

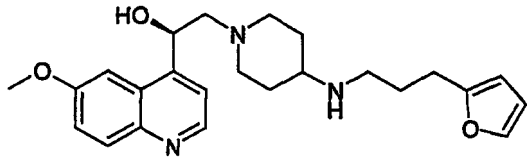
The 3-ethoxycarbonylpiperidine (51c) (50mg) was heated with liquid ammonia (2ml) and potassium cyanide (1-2mg) in methanol (2 ml) at 60°C in a pressure bomb. After 48 hours, more ammonia was added and heating continued for 48 hours. The mixture was evaporated and the residue was dissolved in dichloromethane, washed with water, dried and evaporated. Chromatography on silica gel (methanol-dichloromethane) gave the free base (12mg).

^{1}H NMR ($CDCl_3$): δ 1.60 (0.5H, broad d), 1.7-2.0 (1.5H, m), 2.15 (0.5 H,d), 2.3-2.5 (2H, m), 2.5-2.65(2H, m), 2.65-2.8 (2H, m), 2.82 (0.5H, m), 2.96 (1H, m), 3.16 (0.5H, broad d), 3.35-3.6 (3H, m), 3.89 & 3.90 (3H, 2s), 5.40 & 5.54(1H,2 dd), 5.94 & 6.04 (1H, 2 broad s), 6.17 (1H, dt), 6.21 (1H, m), 6.37 (2H, m), 7.12 & 7.19(1H, 2d), 7.31 (1H, m), 7.35 (1H, s), 7.58 & 7.63(1H, 2d), 8.00(1H, dd), 8.72 (1H, m), 9.14 & 9.34(1H,2 broad s).

MS (+ve ion electrospray) m/z 451 (MH+).

The free base was converted into the dioxalate salt by the method of Example 1.

Example 52. 4-[3-(2-Furyl)-propyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



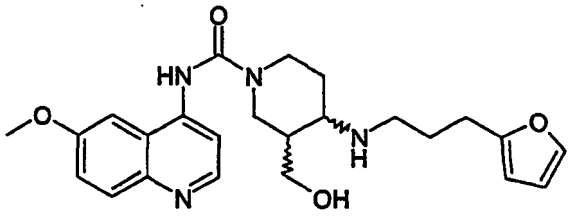
A solution of Example (48) (120mg) in ethanol (10ml) was hydrogenated over 10% palladium/charcoal (20mg) for 3 hours. After filtration and evaporation of solvent, the crude product was chromatographed on silica gel (methanol-dichloromethane) to give the free base (80mg).

^{1}H NMR ($CDCl_3$): δ 1.92(2H,m), 2.19(5H,m), 2.35(1H,t), 2.56(1H, dd), 2.76(2H,t), 2.89(4H,m), 3.35(1H,d), 3.93(3H,s), 5.46(1H,d), 6.07(1H,d), 6.28(1H,m), 7.16(1H,d), 7.31(d), 7.36(1H,dd), 7.63(1H,d), 8.03(1H,d), 8.77(1H,d).

MS (+ve ion electrospray) m/z 410 (MH+).

The free base was converted into the dioxalate salt by the method of Example 1

Example 53. *cis*-4-(S/R)-[3-(2-Furyl)-propyl]amino-3-(R/S)-hydroxymethyl-[6-methoxyquinolin-4-yl)]aminocarbonylpiperidine oxalate



(a) cis-3-(R/S)-Ethoxycarbonyl-4-(S/R)-[trans-1-(2-furyl)-3-propenyl]amino-1-(6-methoxyquinolin-4-yl)aminocarbonylpiperidine

This was prepared from 4-amino-6-methoxyquinoline (Example 5a) and cis-3-(R/S)-Ethoxycarbonyl-4-(S/R)-[trans-1-(2-furyl)-3-propenyl]amino piperidine (Example 51b) by urea formation by the method of Example (5b,c).

MS (+ve ion electrospray) m/z 479 (MH+).

(b) Title compound.

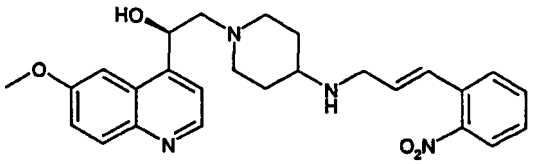
The ester (53a) (90mg) in THF (2ml) was treated with lithium aluminium hydride (1M in THF, 0.4ml) at 0°C. After 4 hours the mixture was treated with dilute sodium hydroxide, diluted with ethyl acetate, dried, filtered and evaporated. Chromatography on silica gel (methanol-dichloromethane) gave a mixture of 1-(2-furyl)-3-propenylamino and 3-(2-furyl)propylamino compounds, which was hydrogenated in ethanol over 10% palladium-charcoal for 6 hours to give the title compound free base (26mg).

^{1}H NMR (CD_3OD): δ 1.59(2H,m), 1.87(3H,m), 2.29(1H, broad), 2.70(3H,m), 3.03(2H,m), 3.18(1H,d), 3.55-3.7(2H,m), 3.86(2H,m), 3.93(3H,s), 4.36(2H,t), 6.06(1H,d), 6.29(1H,d), 7.342H,m), 7.50(1H,d), 7.76(1H,d), 7.84(1H,d), 8.48(1H,d).

MS(+ve ion electrospray) m/z 439 (MH+).

The free base was converted into the oxalate salt by the method of Example 1

Example 54. 4-[*trans*-1-(2-Nitrophenyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



This compound was prepared from the aminopiperidine (Example 13c) (0.6g) and *trans*-2-nitrocinnamaldehyde (0.25g) by the method of Example (43) to give the free base (0.65g).

^{1}H NMR ($CDCl_3$): δ 1.49 (2H, m), 2.00 (2H, broad t), 2.25 (1H, td), 2.39-2.70 (3H, m), 2.85 (2H, m), 3.29 (1H, m), 3.52 (2H, d), 3.94 (3H, s), 5.44 (1H, dd), 6.28 (1H, dt), 7.01 (1H, d), 7.19 (1H, d), 7.39 (2H, m), 7.59 (2H, m), 7.64 (1H, d), 7.93 (1H,d), 8.04(1H, d), 8.78 (1H, d).

MS (+ve ion electrospray) m/z 463 (MH+).
The free base was converted into the dioxalate salt by the method of Example 1.

Example 55. 4-[*trans*-3-(2-Aminophenyl)-propyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This compound was prepared from Example (54) by hydrogenation over 10% palladium on charcoal, converting to the dioxalate salt (52mg) by the same procedure as for Example (1)
MS (+ve ion electrospray) m/z 435 (MH+)

Example 56. 4-[2-(2-Fluorophenoxy)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared by the same procedure as for Example (43),
MS (+ve ion electrospray) m/z 440 (MH+)

Example 57. 4-[2-(4-Fluorophenoxy)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared by the same procedure as for Example (43),
MS (+ve ion electrospray) m/z 440 (MH+)

Example 58. 4-[2-(3-Trifluoromethylphenoxy)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared from ketone (1c) and 2-(3-trifluoromethylphenoxy)-ethylamine according to the same procedure as Example (44) . The free base was converted to the dioxalate salt by the same procedure as Example (1).
MS (+ve ion electrospray) m/z 490 (MH+)

Example 59. 4-[2-(Pyridin-3-yloxy)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared by the same procedure as for Example (45).
MS (+ve ion electrospray) m/z 423 (MH+)

Example 60. 4-[2-(Pyridin-4-yloxy)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared by a similar procedure to Example (45).
MS (+ve ion electrospray) m/z 423 (MH+)

Example 61. 4-[2-(4-Cyanophenoxy)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared by the same procedure as for Example (43).

MS (+ve ion electrospray) m/z 447 (MH+)

Example 62. 4-[2-(Pyrimidin-2-yloxy)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared by a similar procedure to Example (45).

MS (+ve ion electrospray) m/z 424 (MH+)

Example 63. 4-[(*trans*-1-(4-Fluorophenyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared from 4-fluorophenylcinnamaldehyde by the same procedure as for Example (48).

MS (+ve ion electrospray) m/z 436 (MH+)

Example 64. 4-[*trans*-1-(2-Methoxyphenyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared from 2-methoxycinamaldehyde by the same procedure as for Example (48).

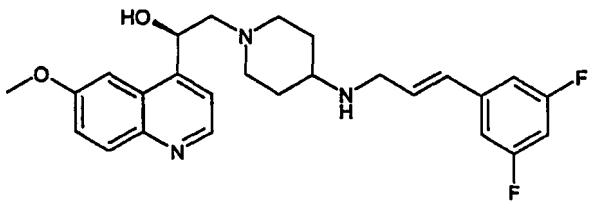
MS (+ve ion electrospray) m/z 448 (MH+)

Example 65. 4-[*trans*-1-(4-Methoxyphenyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

This was prepared using 4-methoxycinnamaldehyde by the same procedure as for Example (48).

MS (+ve ion electrospray) m/z 448 (MH+)

Example 66. 4-{*trans*-1-[3,5-Difluorophenyl]-3-propenyl}amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



(a) (*trans*)-3-(3,5-Difluorophenyl)-prop-2-en-1-ol

A solution of (trans)-3-(3,5-difluorophenyl)-acrylic acid (1g) in tetrahydrofuran (10 ml) was treated at 0°C with triethylamine (0.9 ml), then *iso*butyl chloroformate (0.8 ml) was added dropwise. After 1 hour, the mixture was filtered and the filtrate diluted with ice/water (10 g). Sodium borohydride (0.5g) was added. After 3 hours, 2M aqueous hydrochloric acid was added. The mixture was partitioned between dichloromethane and brine. The organic extract was dried and evaporated. Chromatography on silica gel (ethyl acetate-hexane) afforded the alcohol as an oil (0.4g). (See R. J. Alabaster *et al*, Synthesis 1989, 598 for a related procedure.)

MS (+ve ion electrospray) m/z 171 (MH+)

(b) (*trans*)-3-(3,5-Difluorophenyl)-propenal

A solution of (66a) (0.2g) in dichloromethane (3 ml) was treated with manganese (II) dioxide (0.52g). After 16 hours, the mixture was filtered and evaporated to give the aldehyde as a white solid (0.18g).

MS (+ve ion electrospray) m/z 169 (MH+)

(c) Title compound

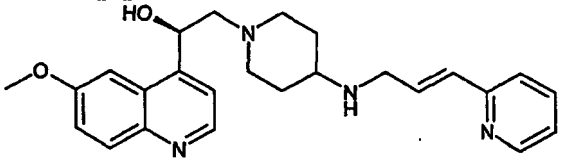
This was prepared from aldehyde (66b) (0.73g) and amine (13c) (0.1g) by reductive alkylation using sodium borohydride using the same procedure as for Example 48, giving the title compound as an oil (0.08g) after chromatography.

^{1}H NMR ($CDCl_3$) δ: 1.55 (2H, m), 2.00 (2H, m), 2.25(1H, m), 2.40-2.65 (3H, m), 2.85(2H, m), 3.30 (1H, m), 3.50 (2H, d), 3.90 (3H, s), 5.45 (1H, dd), 6.30 (1H, m), 6.45 (1H, d),), 6.65 (1H, m),), 6.85 (2H, m),7.15 (1H, m), 7.35 (1H, dd), 7.65 (1H, d), 8.05 (1H, d), 8.75 (1H, d)

MS (+ve ion electrospray) m/z 454 (MH+)

The free base was converted to the dioxalate in the normal manner.

Example 67. 4-{*trans*-1-[Pyridin-2-yl]-3-propenyl}amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

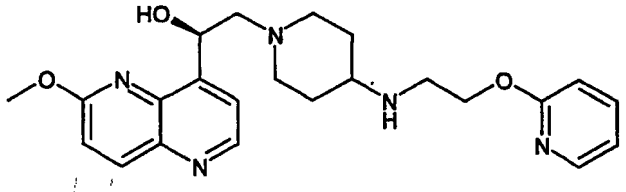


This was prepared from (*trans*)-3-pyridin-2-yl-acrylic acid by the same procedure as for Example (66).

^{1}H NMR ($CDCl_3$) δ: 1.55 (2H, m), 2.00 (2H, m), 2.25(1H, m), 2.35-2.70 (3H, m), 2.85(2H, m), 3.28 (1H, m), 3.55 (2H, d), 3.90 (3H, s), 5.45 (1H, dd), 6.68 (1H, m), 6.80 (1H, m),7.15 (2H, m), 7.25-7.40 (2H, m), 7.65 (2H, m), 8.05 (1H, d), 8.50 (1H, d) 8.78 (1H, d)

MS (+ve ion electrospray) m/z 419 (MH+)
The free base was converted to the dioxalate in the normal manner.

Example 68 (R)-1-(6-Methoxy-[1,5]naphthyridin-4-yl)-2-{4-[2-(pyridin-2-yloxy)-ethylamino]-piperidin-1-yl}-ethanol dioxalate

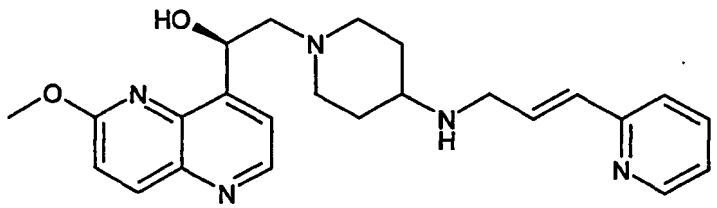


(a) 1-[(R)-2-Hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-piperidin-4-one

This was prepared by reaction of the naphthyridine oxirane (31d) with 1,4-dioxa-8-azaspiro-[4,5]-decane, followed by acidic hydrolysis of the ketal to give the ketone, by the same procedures as for Example (1c).
MS (+ve ion electrospray) m/z 302 (MH+).
(b) Title compound

This was prepared by reductive alkyation of the above ketone (68a) with 2-(pyridin-2-yloxy)-ethylamine according to the procedure for Example 45, affording the title compound as an oil (62 mg, 55%).
^{1}H NMR ($CDCl_3$) δ: 1.55 (2H, m), 2.00 (2H, m), 2.25(1H, m), 2.35-2.70 (3H, m), 2.85(2H, m), 3.05-3.15 (3H, m), 3.30 (1H, m), 3.95 (3H, s), 4.45 (2H, t),5.70 (1H, dd) 6.75 (1H, m), 6.85 (1H, m),7.15 (1H, d), 7.55 (1H, m), 7.85 (1H, d), 8.15 (1H, m), 8.20 (1H, d) 8.78 (1H, d)
MS (+ve ion electrospray) m/z 424 (MH+)
The free base was converted to the dioxalate in the normal manner.

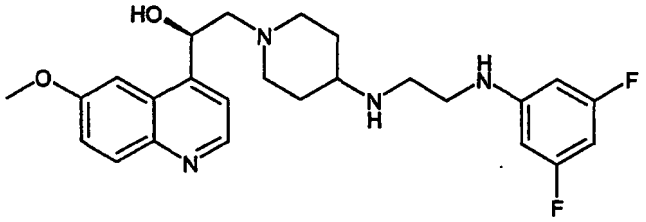
Example 69 (R)-1-(6-Methoxy-[1,5]naphthyridin-4-yl)-2-[4-((E)-3-pyridin-2-yl-allylamino)-piperidin-1-yl]-ethanol dioxalate salt



This was prepared by reductive alkylation of the amine (31f) with aldehyde (66b) according to the procedures of Example 66, affording an oil (35 mg, 32%)

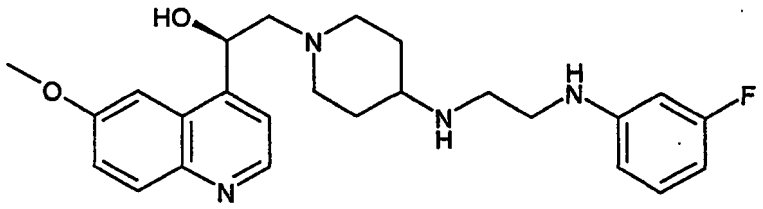
^{1}H NMR ($CDCl_3$) δ: 1.55 (2H, m), 2.00 (2H, m), 2.25(1H, m), 2.35-2.70 (3H, m), 2.85(2H, m), 3.28 (1H, m), 3.55 (2H, d), 4.00 (3H, s), 5.45 (1H, dd), 6.66 (1H, m), 6.75 (1H, m),7.15 (2H, m), 7.30 (1H, m), 7.65 (1H, dt), 7.80 (1H, d), 8.20 (1H, d), 8.55 (1H, d) 8.78 (1H, d)
MS (+ve ion electrospray) m/z 420 (MH+)
The free base was converted to the dioxalate in the normal manner.

Example 70. 4-[2-(3,5-Difluorophenylamino)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



A solution of Example 29 (0.16g) in tetrahydrofuran (5 ml) was treated with a solution of lithium aluminium hydride in tetrahydrofuran (1M; 1.4 ml, 1.4 mmol). After 7h the mixture was treated with 8% aqueous sodium hydroxide solution, ethyl acetate, and sodium sulphate. Filtration, evaporation and chromatography on silica eluting with a methanol/dichloromethane gradient afforded an oil (38 mg, 25%)
^{1}H NMR ($CDCl_3$) δ: 1.5 (2H, m), 2.00 (2H, m), 2.23(1H, m), 2.35-2.60 (3H, m), 2.80-2.95(4H, m), 3.10-3.30 (3H, m), 3.92 (3H, s), 4.48 (1H, bs), 5.43 (1H, dd), 6.13 (3H, m), 7.19 (1H, d), 7.38 (1H, dd), 7.69 (1H, d), 8.04 (1H, d), 8.78 (1H, d)
MS (+ve ion electrospray) m/z 457 (MH+)
The free base was converted to the dioxalate in the normal manner.

Example 71. 4-[2-(3-Fluorophenylamino)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



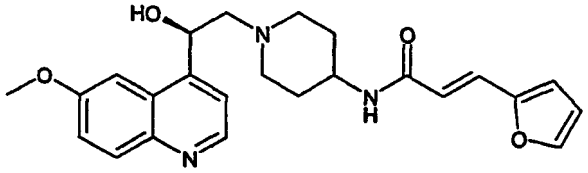
(a) 2-(3-Fluorophenylamino)-ethylamine

A mixture of 3-fluoroaniline (1g, 9 mmol), 2-bromoethylamine hydrobromide (1.8g, 9 mmol) and toluene (10 ml) was heated to reflux under argon for 8h. The toluene was decanted off and the residue dissolved in water, basified with potassium hydroxide

and extracted with dichloromethane. The dichloromethane extracts were dried (sodium sulphate) and evaporated to give an oil. Chromatography on silica eluting with a methanol/dichloromethane gradient afforded an oil (0.44g, 32%).
MS (+ve ion electrospray) m/z 155 (MH+)
(b) Title compound

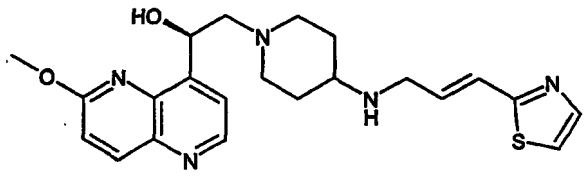
This was prepared by reductive alkylation of amine (71c) and ketone (1c) using sodium triacetoxyborohydride according to the procedure of Example 44, affording the title compound as an oil (0.42g, 79%).
^{1}H NMR ($CDCl_3$) δ: 1.5 (2H, m), 2.00 (2H, m), 2.23(1H, m), 2.35-2.60 (3H, m), 2.80-2.95(4H, m), 3.10-3.30 (3H, m), 3.94 (3H, s), 4.40 (1H, bs), 5.45 (1H, dd), 6.30-6.50 (3H, m), 7.15(1H, m), 7.20(1H, d), 7.40 (1H, dd), 7.70 (1H, d), 8.08 (1H, d), 8.78 (1H, d)
MS (+ve ion electrospray) m/z 439 (MH+)
The free base was converted to the dioxalate in the normal manner.

Example 72 (E)-3-Furan-2-yl-N-{1-[(R)-2-hydroxy-2-(6-methoxyquinolin-4-yl)-ethyl]-piperidin-4-yl}-acrylamide oxalate



To a solution of (E)-3-furan-2-ylacrylic acid (28mg, 0.2 mmol) and di-isopropylethylamine (0.07 ml, 0.4 mmol) in N,N-dimethylformamide (0.2 ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (38mg, 0.2mmol) in dry dichloromethane (1.5 ml) and aminopiperidine (13c), (50mg, 0.17mmol) in dry dichloromethane (1 ml). The mixture was shaken for a short period then allowed to stand overnight. The mixture was then washed well with water, dried and evaporated. The crude product was chromatographed on silica gel eluted with 0-5% methanol/dichloromethane to give the free base of title compound (46mg, 64%).
^{1}H NMR ($CDCl_3$) δ 1.6 (2H, m), 2.09 (2H, m), 2.34 (1H, m), 2.53 (2H, m), 2.82 (1H, m), 2.87 (1H, dd), 3.27 (1H,m) 3.93 (3H,s & 1H, m), 5.45 (1H, dd), 5.59 (1H, d), 6.29 (1H, d), 6.47 (1H, m), 6.56 (1H, d), 7.17 (1H, d), 7.38 (1H, dd), 7.44 (2H, m), 7.64 (1H, d), 8.04 (1H, d), 8.78 (1H, d)
MS (+ve ion electrospray) m/z 422 (MH+).
The free base in chloroform/dichloromethane was treated with one equivalent of oxalic acid in ether to give the oxalate salt.

Example 73. 4-[*trans*-1-(2-Thiazolyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxy-[1,5]-naphthyridin-4-yl)]ethylpiperidine dimethanesulphonate



(a) (E)-3-Thiazol-2-yl-propenal

A mixture of formylmethylene triphenylphosphorane (0.9g) and thiazole-2-carboxaldehyde (0.33g) in toluene (20 ml) was heated at 40°C for 4h. The mixture was chromatographed on silica eluting with an ethyl acetate-dichloromethane gradient affording a white solid (0.25g).

^{1}H NMR ($CDCl_3$): δ 6.90 (1H, dd), 7.55 (1H, d), 7.65 (1H, d), 8.00 (1H, d), 9.75 (1H, d)
MS (+ve ion electrospray) m/z 140 (MH+)

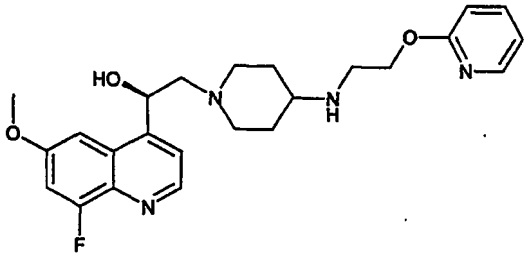
(b) Title compound

This was prepared by reductive alkylation of amine (31f) and aldehyde (73a) according to the procedure of Example 48 affording the free base of the title compound as an oil (0.4g, 80%).

^{1}H NMR ($CDCl_3$): δ: 1.45-1.55 (2H, m), 1.90-2.05 (2H, m), 2.20 (1H, m), 2.40-3.10 (5H, m), 3.60 (2H, d), 4.05 (3H, s), 5.75 (1H, dd), 6.68 (1H, t), 6.80 (1H, s), 7.10 (1H, d), 7.20 (1H, d), 7.73 (1H, d), 7.80 (1H, d), 8.20 (1H, d), 8.78 (1H, d)
MS (+ve ion electrospray) m/z 426 (MH+)

This was converted to the dimethanesulphonate salt by adding an ether solution of methanesulphonic acid (2 equivalents) to a solution of the free base in chloroform, followed by isolation by centrifugation (0.45g).

Example 74. 4-[2-(Pyridin-2-yloxy)-ethylamino]-1-[2-(R)-hydroxy-2-(8-fluoro-6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



(a) 8-Fluoro-6-methoxy-quinolin-4-ol

2-Fluoro-4-methoxy-phenylamine (3.80g;26.7mmol) and methyl propiolate (2.37ml, 0.267mol) in methanol (100ml) was stirred for 72 hours at room temperature, then heated at 50°C for 24 hours. It was evaporated and the product purified by chromatography on silica gel (dichloromethane) to give a solid (1.66g), a portion of which was recrystallised from dichloromethane-hexane.

The unsaturated ester (0.96g) in warm Dowtherm A (5ml) was added over 3 minutes to refluxing Dowtherm A (15ml), and after a further 20 minutes at reflux the mixture was cooled and poured into ether. The precipate was filtered to give the title compound (0.50g, 61%)

(b) Bromomethyl-(8-fluoro-6-methoxy-quinolin-4-yl)-ketone

This was prepared from (74a) by the method of Example (31b).

MS (+ve ion electrospray) m/z 298/300 (MH+).

(c) 8-Fluoro-6-methoxy-4-(R)-oxiranyl-quinoline

The bromomethyl ketone (74b) (8.6g) was converted to the oxirane (1.04g) by the methods of Examples (31c,d).

MS (+ve ion electrospray) m/z 220 (MH+).

(d) 1-[(R)-2-(8-Fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-piperidin-4-one

This was prepared from oxirane (74c) (1.04g) by the method of Example (1b,c) to give the ketone (1.1g) as a foam.

MS (+ve ion electrospray) m/z 319 (MH+).

(e) Title compound

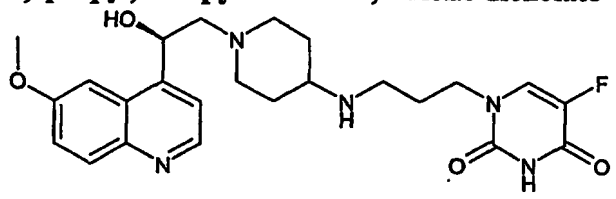
This was prepared from ketone (74d) and amine (45a) according to the procedure of Example 45, affording the free base as an oil (84 mg, 65%).

^{1}H NMR ($CDCl_3$) δ: 1.60 (2H, m), 1.95 (2H, m), 2.15 (1H, m), 2.50 (3H, m), 2.80 (2H, m), 3.08 (2H, t), 3.25 (1H, m), 3.95 (3H, s), 4.45 (2H, t), 5.45 (1H, dd), 6.75 (1H, d), 6.85 (1H, m), 7.00 (1H, m), 7.15 (1H, m), 7.40 (1H, dd), 7.60 (1H, m), 7.70 (1H, m), 8.15 (1H, m), 8.80 (1H, d).

MS (+ve ion electrospray) m/z 441 (MH+).

This was converted to the dioxalate salt (112 mg) in the usual way

Example 75. 5-Fluoro-1-(3-{1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidin-4-ylamino}-propyl)-1*H*-pyrimidine-2,4-dione dioxolate



(a) 1-(3,3-Dimethoxy-propyl)-5-fluoro-1*H*-pyrimidine-2,4-dione

A mixture of 5-fluoro-1H-pyrimidine-2,4-dione (1 g), potassium carbonate (1 g) and 3-bromo-1,1-dimethoxy-propane (1.4 g) in N,N-dimethylformamide (10 ml) was heated overnight at 70°C. The mixture was partitioned between ether and water. The ether extract was dried and evaporated to afford an oil (0.8gg).

MS (+ve ion electrospray) m/z 233 (MH+).

(b) 3-(5-Fluoro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionaldehyde

The above compound was dissolved in a 2% solution of water in tetrahydrofuran (5 ml), treated with acidic Amberlyst-15 resin (0.75g) and heated at 60°C for 10 hours. The mixture was filtered and evaporated affording the aldehyde as an oil (0.2g).
MS (+ve ion electrospray) m/z 187 (MH+)

(c) Title compound

This was prepared from aldehyde (75b) (0.2g) and aminopiperidine (13c) (0.15g) by reductive alkylation according to the procedure of Example 43b to give the title compound as an oil (23 mg)
^{1}H NMR (d-6 MeOH) δ 1.6-1.8 (2H, m), 2.0-2.2 (4H, m), 2.3-2.4 (2H, m), 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.2-3.3 (2H, m), 3.7 (1H, m), 3.8 (2H, m), 3.95 (3H, s), 5.60 (1H, m), 7.30-7.40 (2H, m), 7.65 (1H, d, 7.85 (1H, d), 7.95 (1H, d), 8.65 (1H, d)
MS (+ve ion electrospray) m/z 472 (MH+)

This was converted to the dioxolate salt (30 mg) in the usual way

The following Examples of Table 1 were prepared by analogous methods.

A: by method of Example 43

B: by method of Example 55

C: by method of Example 62

D: by method of Example 48

E: by method of Example 52

F: by method of Example 44

G: by method of Example 71

H: by method of Example 45

I: by method of Example 70

J: by method of Example 13

K: by method of Example 1

L: by method of Example 33

M: Prepared in ca 2% yield by alkylation of 4-amino-1-[(R)-2-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperidine-4-carboxylic acid carbamoylmethyl-amide with (E)-(3-bromo-propenyl)-benzene.

N: by method of Example 72

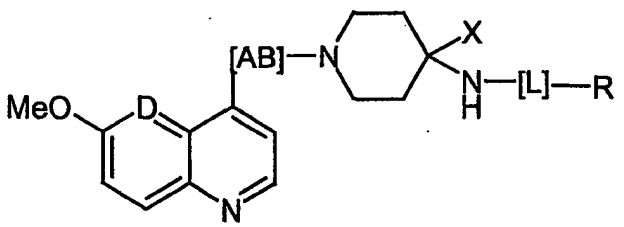
O: by method of Example 75

Salts: AY = dioxalate

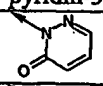
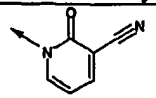
DZ = dimesylate

G = oxalate

Table 1



Example	Method of Synthesis	Isolated as salt	D	AB	X	L	R
200	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3-fluorophenyl
201	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3,4-difluorophenyl
202	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2,3-difluorophenyl
203	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2,5-difluorophenyl
204	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2,4-difluorophenyl
205	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3,4,5-trifluorophenyl
206	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2,3-difluoro-6-nitrophenyl
207	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3,4-dichlorophenyl
208	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-fluoro-6-methylphenyl
209	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-bromo-5-fluorophenyl
210	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-chloro-4-fluorophenyl
211	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-chloro-3-trifluoromethylphenyl
212	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-cyanophenyl
213	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-chloro-3,5-difluorophenyl
214	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-fluoro-6-nitrophenyl
215	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-fluoro-5-trifluoromethylphenyl
216	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	4-fluoro-2-nitrophenyl
217	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-nitrophenyl
218	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-chloro-5-nitromethylphenyl

219	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-methyl-5-fluorophenyl
220	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3-cyanophenyl
221	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3-fluoro-2-nitrophenyl
222	B	KT	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-aminophenyl
223	B	KT	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	6-amino-3-fluorophenyl
224	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-methoxyphenyl
225	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-trifluoromethylphenyl
226	C	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	pyrimidin-5-yl
227	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2,6-difluorophenyl
228	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3,5-dimethoxyphenyl
229	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2,3-dimethoxyophenyl
230	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3-methoxyphenyl
231	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	2-acetamidophenyl
232	A	AY	CH	(R)-CH(OH)CH_2	H	CH_2CH_2O	3-methoxycarbonylphenyl
300	D	DZ	CH	(R)-CH(OH)CH_2	H	(*E*)CH_2CH=CH	thiazol-2-yl
301	E	AY	CH	(R)-CH(OH)CH_2	H	$CH_2CH_2CH_2$	3,5-difluorophenyl
302	D	DZ	CH	(R)-CH(OH)CH_2	H	(*E*)CH_2CH=CH	pyridin-3-yl
303	O	AY	CH	(R)-CH(OH)CH_2	H	$CH_2CH_2CH_2$	
304	O	AY	CH	(R)-CH(OH)CH_2	H	$CH_2CH_2CH_2$	
305	F	AY	CH	(R)-CH(OH)CH_2	H	$CH_2CH_2CH_2$	3-imidazol-l-yl
306	O	AY	CH	(R)-CH(OH)CH_2	H	$CH_2CH_2CH_2$	
307	D	AY	CH	(R)-CH(OH)CH_2	H	(*E*)CH_2CH=CH	4-dimethylaminophenyl
308	F	AY	CH	(R)-CH(OH)CH_2	H	$CH_2CH_2CH_2$	1-*H*-[1,2,4]triazol-5-yl
309	A	AY	CH	(R)-CH(OH)CH_2	H	$CH_2CH_2CH_2$	4-fluorophenyl
310	A	AY	N	(R)-CH(OH)CH_2	H	CH_2CH_2O	3,5-difluorophenyl

311	M	G	CH	(R)-$CH(OH)CH_2$	$CONHCH_2CONH_2$	(*E*)CH_2CH=CH	phenyl
400	A	S	CH	NHCO	H	CH_2CH_2O	3,5-difluorophenyl
401	A	G	N	NHCO	H	CH_2CH_2O	3,5-difluorophenyl
402	H	AY	N	NHCO	H	CH_2CH_2O	pyridin-2-yl
403	D	AY	N	NHCO	H	(*E*)CH_2CH=CH	pyridin-2-yl
404	I	AY	N	NHCO	H	CH_2CH_2NH	3,5-difluorophenyl
405	G	AY	N	NHCO	H	CH_2CH_2NH	3-fluorophenyl
500	F	DZ	CH	(R)-$CH(OH)CH_2$	H	CH_2CH_2NH	6-fluoropyridin-2-yl
501	F	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CH_2NH	phenyl
502	F	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CH_2NH	3-trifluoromethylpyridin-2-yl
503	F	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CHNH	pyridin-2-yl
504	F	G	CH	(R)-$CH(OH)CH_2$	H	CH_2CH_2NH	4-azido-2-nitrophenyl
505	F	G	CH	(R)-$CH(OH)CH_2$	H	CH_2CH_2NH	5-nitropyridin-2-yl
506	F	G	CH	(R)-$CH(OH)CH_2$	H	CH_2CH_2NH	6-nitropyridin-2-yl
507	F	AY	N	(R)-$CH(OH)CH_2$	H	CH_2CH_2NH	3-fluorophenyl
601	J	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CONH	3-fluorophenyl
602	J	AY	N	(R)-$CH(OH)CH_2$	H	CH_2CONH	pyrid-2-yl
603	J	AY	N	(R)-$CH(OH)CH_2$	H	CH_2CONH	3,5-difluorophenyl
604	K	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CONH	pyrazyl
605	J	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CONH	6-methylpyrid-2-yl
606	J	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CONH	3-methoxyphenyl
607	J	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CONH	2-*n*-butylphenyl
608	J	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CONH	3-*n*-butylaminosulphonylphenyl
609	L	AY	CH	(R)-$CH(OH)CH_2$	H	CH_2CONH	3-carboxyphenyl
610	N	AY	CH	(R)-$CH(OH)CH_2$	H	*E*-COCH=CH	3,5-difluorophenyl
611	N	AY	CH	(R)-$CH(OH)CH_2$	H	*E*-COCH=CH	3-thienyl
612	N	AY	CH	(R)-$CH(OH)CH_2$	H	*E*-COCH=CH	3-bromo-5-fluorophenyl

613	N	AY	CH	(R)-CH(OH)CH_2	H	*E*-COCH=CH	3-fluoro-pyridin-2-yl
614	N	G	CH	(R)-CH(OH)CH_2	H	*E*-COCH=CH	2-nitrophenyl
615	N	-G	CH	(R)-CH(OH)CH_2	H	$COCH_2O$	phenyl
616	J	DZ	CH	(R)-CH(OH)CH_2	H	CH_2CONH	3-hydroxypheayl

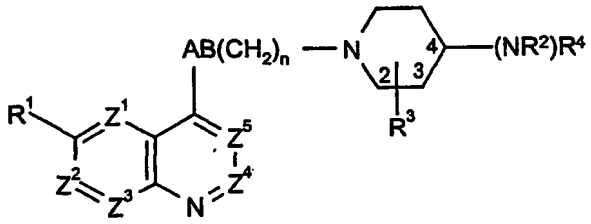
Biological Activity

The MIC (μg/ml) of test compounds against various organisms was determined: **S. aureus Oxford, S. aureus WCUH29, S. pneumoniae 1629, S. pneumoniae N1387, S. pneumoniae ERY 2, E. faecalis 1, E. faecalis 7, H. influenzae Q1, H. influenzae NEMC1, M. catarrhalis 1502, E. coli 7623, E.coli 120.**

Examples 1, 2 , 13, 17, 19, 20, 29, 43-52, 54, 56-58, 63, 66-71, 73, 74, 200-217, 219, 221, 222, 225, 300, 301 304, 310, 401, 404, 500, 501, 507, 601-604 have an MIC of less than or equal to 0.25μg/ml; 3,4,11, 18,21-25, 38, 41, 42, 53, 55, 59, 62, 64, 72, 218, 220, 223, 224, 231, 302, 303, 402, 403, 405, 502-504, 506, 605, 606, 610-614 have an MIC of less than or equal to 2μg/ml; 5,6, 12, 26-28, 34, 36, 37, 75, 226-230, 232, 311, 400, 505, 607-610 have an MIC less than or equal to 32μg/ml; others have an MIC level >32ug/ml against one or more of the above range of gram positive and gram negative bacteria.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, one is CR^{1a} and the remainder are CH , or one or two of Z^1, Z^2, Z^3, Z^4 and Z^5 are independently CR^{1a} and the remainder are CH;

R^1 and R^{1a} are independently hydrogen; hydroxy; (C_{1-6})alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; trifluoromethoxy; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

provided that when Z^1, Z^2, Z^3, Z^4 and Z^5 are CR^{1a} or CH, then R^1 is not hydrogen;

R^2 is hydrogen, or (C_{1-4})alkyl or (C_{2-4})alkenyl optionally substituted with 1 to 3 groups selected from:
amino optionally substituted by one or two (C_{1-4})alkyl groups; carboxy; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, aminocarbonyl(C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-4})alkenylsulphonyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl or (C_{2-4})alkenylcarbonyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-

ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; 5-oxo-1,2,4-oxadiazol-3-yl; halogen; (C_{1-4})alkylthio; trifluoromethyl; hydroxy optionally substituted by (C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl; oxo; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or (C_{1-4})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

R^3 is hydrogen; or
R^3 is in the 2-, 3- or 4-position and is:
carboxy; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; or 5-oxo-1,2,4-oxadiazol-3-yl; or
(C_{1-4})alkyl or ethenyl optionally substituted with any of the substituents listed above for R^3 and/or 0 to 2 groups R^{12} independently selected from:

halogen; (C_{1-6})alkylthio; trifluoromethyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or when R^3 is in the 3-position, hydroxy optionally substituted as described above;

in addition when R^3 is disubstituted with a hydroxy or amino containing substituent and carboxy containing substituent these may together form a cyclic ester or amide linkage, respectively;

R^4 is a group $-X^1-X^2-X^3-X^4$ in which:

X^1 is CH_2, CO or SO_2;

X^2 is $CR^{14}R^{15}$;

X^3 is NR^{13}, O, S, SO_2 or $CR^{14}R^{15}$; wherein:

each of R^{14} and R^{15} is independently selected from: hydrogen; halo; (C_{1-4})alkoxy; (C_{1-4})alkylthio; trifluoromethyl; cyano; carboxy; nitro; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally mono- or di-substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl, provided that R^{14} and R^{15} on the same carbon atom are not both selected from optionally substituted hydroxy and optionally substituted amino; or

R^{14} and R^{15} together represent oxo;

R^{13} is hydrogen; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

two R^{14} groups or an R^{13} and an R^{14} group on adjacent atoms together represent a bond and the remaining R^{13}, R^{14} and R^{15} groups are as above defined;

two R^{14} groups and two R^{15} groups on adjacent atoms together represent bonds such that X^2 and X^3 is triple bonded;

two R^{14} groups or an R^{13} and an R^{14} group in X^2 and X^3 together with the atoms to which they are attached form a 5 or 6 membered carbocyclic or heterocyclic ring and the remaining R^{15a} groups are as above defined;

X^4 is phenyl or C or N linked monocyclic aromatic 5- or 6-membered heterocycle containing up to four heteroatoms selected from O, S and N and optionally C-substituted by up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy;

hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy; and
optionally N substituted by trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

n is 0 or 1;

A is NR^{11}, O or CR^6R^7 and B is NR^{11}, O, SO_2 or CR^8R^9 and wherein:
each of R^6, R^7, R^8 and R^9 is independently selected from: hydrogen; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;
or when n=1 R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;
or R^6 and R^7 or R^8 and R^9 together represent oxo;

provided that:
when A is NR^{11}, B is not NR^{11} or O;
when A is CO, B is not CO, O or SO_2;
when n is 0 and A is NR^{11}, CR^8R^9 can only be CO;
when A is CR^6R^7 and B is SO_2, n is 0;
when n is 0, B is not NR^{11} or O or R^8 and R^9 are not optionally substituted hydroxy or amino;
when A is O, B is not NR^{11}, O, SO_2 or CO and n=1; and
when A-B is CR^7=CR^9, n is 1

R^{10} is selected from (C_{1-4})alkyl; (C_{2-4})alkenyl and aryl any of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; (C_{1-6})alkylsulphonyl; trifluoromethylsulphonyl; (C_{2-6})alkenylsulphonyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; and (C_{2-6})alkenylcarbonyl; and

R^{11} is hydrogen; trifluoromethyl, (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage.

2. A compound according to claim 1 wherein Z^5 is CH or N, Z^3 is CH or CF and Z^1, Z^2 and Z^4 are each CH, or Z^1 is N, Z^3 is CH or CF and Z^2, Z^4 and Z^5 are each CH.

3. A compound according to any preceding claim wherein R^1 is methoxy and R^{1a} is H or when Z^3 is CR^{1a} it may be C-F.

4. A compound according to any preceding claim wherein R^2 is hydrogen, carboxymethyl, hydroxyethyl, aminocarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylallyl or carboxyallyl.

5. A compound according to any preceding claim wherein R^3 is hydrogen; optionally substituted hydroxy; (C_{1-4}) alkyl; ethenyl; optionally substituted 1-hydroxy-(C_{1-4}) alkyl; optionally substituted aminocarbonyl; carboxy(C_{1-4})alkyl; optionally substituted aminocarbonyl(C_{1-4})alkyl; cyano(C_{1-4})alkyl; optionally substituted 2-oxo-oxazolidinyl and optionally substituted 2-oxo-oxazolidinyl$(C_{1-4}$alkyl); in the 3- or 4-position.

6. A compound according to any preceding claim wherein n is 0, A-B is CHOH-CH_2, NR^{11}-CH_2 or NR^{11}-CO and R^{11} is hydrogen or (C_{1-4})alkyl.

7. A compound according to any preceding claim wherein $-X^1-X^2-X^3-$ is $-(CH_2)_2-O-$, $-CH_2-CH=CH-$, $-(CH_2)_3-$, $-(CH_2)_2-NH-$ or $-CH_2CONH-$.

8. A compound according to any preceding claim wherein X^4 is 2-pyridyl, 3-fluorophenyl, 3,5-difluorophenyl or thiazol-2-yl.

9. A compound according to claim 1 selected from:
2-{1-[(R)-2-Hydroxy-2-(6-methoxy-[1,5]-naphthyridine-4-yl)-ethyl]-piperidin-4-ylamino}-N-phenyl-acetamide;
4-{*trans*-1-[3,5-Difluorophenyl]-3-propenyl}amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine;
(R)-1-(6-Methoxy-[1,5]naphthyridin-4-yl)-2-{4-[2-(pyridin-2-yloxy)-ethylamino]-piperidin-1-yl}-ethanol;
(R)-1-(6-Methoxy-[1,5]naphthyridin-4-yl)-2-[4-((E)-3-pyridin-2-yl-allylamino)-piperidin-1-yl]-ethanol;
4-[2-(3,5-Difluorophenylamino)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine;
4-[2-(3-Fluorophenylamino)-ethyl]amino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine; and
4-[*trans*-1-(2-thiazolyl)-3-propenyl]amino-1-[2-(R)-hydroxy-2-(6-methoxy-[1,5]-naphthyridin-4-yl)]ethylpiperidine
or a pharmaceutically acceptable derivative thereof.

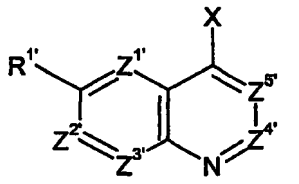
10. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound according to claim 1.

11. The use of a compound according to claim 1, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

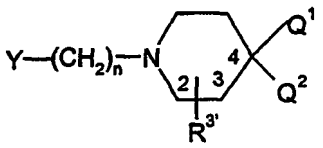
12. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.

13. A process for preparing compounds according to claim 1, which process comprises:

reacting a compound of formula (IV) with a compound of formula (V):



(IV)

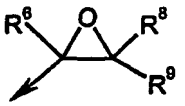


(V)

wherein n is as defined in formula (I); $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$ and $R^{3'}$ are Z^1, Z^2, Z^3, Z^4, Z^5, R^1 and R^3 as defined in formula (I) or groups convertible thereto;
Q^1 is NR^2R^4 or a group convertible thereto wherein $R^{2'}$ and $R^{4'}$ are R^2 and R^4 as defined in formula (I) or groups convertible thereto and Q^2 is H or $R^{3'}$ or Q^1 and Q^2 together form an optionally protected oxo group;
and X and Y may be the following combinations:

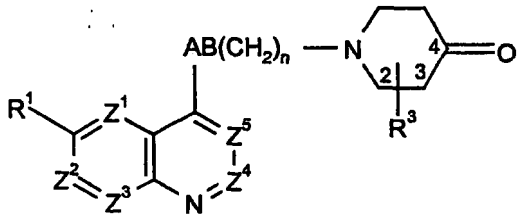
(i) X is A'-COW, Y is H and n is 0;
(ii) X is $CR^6{=}CR^8R^9$, Y is H and n is 0;
(iii) X is oxirane, Y is H and n is 0;
(iv) X is N=C=O and Y is H and n is 0;
(v) one of X and Y is CO_2R^Y and the other is $CH_2CO_2R^X$;
(vi) X is CHR^6R^7 and Y is $C(=O)R^8$;
(vii) X is $CR^7{=}PR^z{}_3$ and Y is $C(=O)R^9$ and n=1;
(viii) X is $C(=O)R^7$ and Y is $CR^9{=}PR^z{}_3$ and n=1;
(ix) Y is COW and X is $NHR^{11'}$ or NCO or $NR^{11'}COW$ and n=0 or 1 or when n=1 X is COW and Y is $NHR^{11'}$, NCO or $NR^{11'}COW$;
(x) X is $C(=O)R^6$ and Y is $NHR^{11'}$ or X is $NHR^{11'}$ and Y is $C(=O)R^8$ and n=1;
(xi) X is $NHR^{11'}$ and Y is CR^8R^9W and n=1;
(xii) X is CR^6R^7W and Y is $NHR^{11'}$ or OH and n=1; or
(xiii) X is $CR^6R^7SO_2W$ and Y is H and n=0;
(xiv) X is W or OH and Y is CH_2OH and n is 1;
(xv) X is $NHR^{11'}$ and Y is SO_2W or X is $NR^{11'}SO_2W$ and Y is H, and n is 0;
(xvi) X is $NR^{11'}COCH_2W$ and Y is H and n=0;

in which W is a leaving group, e.g. halo or imidazolyl; R^X and R^Y are (C_{1-6})alkyl; R^Z is aryl or (C_{1-6})alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);
and thereafter optionally or as necessary converting Q^1 and Q^2 to $NR^{2'}R^{4'}$; converting A', $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $NR^{11'}$ to A, Z^1, Z^2, Z^3, Z^4, Z^5, R^1, R^2, R^3, R^4 and $NR^{11'}$; converting A-B to other A-B, interconverting R^1, R^2, R^3 and/or R^4, and/or forming a pharmaceutically acceptable derivative thereof.

14. A compound of formula (VI):



(VI)

wherein the variables are as described for formula (I) in claim 1.

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/EP 01/10976

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/06 C07D401/12 C07D401/14 C07D471/04 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 07432 A (SMITHKLINE BEECHAM P.L.C., UK) 1 February 2001 (2001-02-01) cited in the application page 1, line 1-4; claim 1	1-15
A	WO 00 21948 A (HATTON IAN KEITH ;PEARSON NEIL DAVID (GB); SMITHKLINE BEECHAM PLC) 20 April 2000 (2000-04-20) page 1, line 1-5; claim 1	1-15
P,A	EP 1 104 764 A (HOKURIKU SEIYAKU CO., LTD., JAPAN) 6 June 2001 (2001-06-06) examples 49,50,77,78	1
A	& WO 00 09506 A (HOKURIKU SEIYAKU CO.,LTD.,JAPAN) 24 February 2000 (2000-02-24)	1
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2002	12/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Samsam Bakhtiary, M

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/EP 01/10976

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 10

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Inter — al Application No
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(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété Intellectuelle
Bureau international

(43) Date de la publication internationale
23 mai 2002 (23.05.2002)

PCT

(10) Numéro de publication internationale
WO 02/40474 A2

(51) Classification internationale des brevets[7] :
C07D 409/14, 401/06, 401/14, 417/14, A61K 31/47, A61P 31/04

(21) Numéro de la demande internationale :
PCT/FR01/03559

(22) Date de dépôt international :
14 novembre 2001 (14.11.2001)

(25) Langue de dépôt : français

(26) Langue de publication : français

(30) Données relatives à la priorité :
00/14738 15 novembre 2000 (15.11.2000) FR

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(81) États désignés *(national)* : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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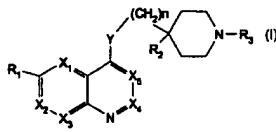
[Suite sur la page suivante]

(54) Title: HETEROCYCLYLALKYL PIPERIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING SAME

(54) Titre : DERIVES HETEROCYCLYLALCOYL PIPERIDINE, LEUR PREPARATION ET LES COMPOSITIONS QUI LES CONTIENNENT



(I)

(57) Abstract: The invention concerns heterocyclylalkyl piperidine derivatives of general formula (I), wherein X_1, X_2, X_3, X_4 and X_5 are >C-R'$_1$ to >C-R'$_5$ or one at most represents N; R_1 is COOH, alkyloxycarbonyl, cycloalkyloxycarbonyl, CN, -CONRaRb or R_2 is CH_2OH, alkyl substituted or R_2 is -CF_2-Rc, -$C(CH_3)_2$-Rc, -CO-Rc, -CHOH-Rc, -C(cycloalkyl)-Rc or -CH=CH-Rc; R_3 is phenyl, heterocyclyl. alk-R"$_3$; Y represents >CH-Re or a difluoromethylene, carbonyl, hydroxyiminomethylene, alkyloxyiminomethylene, cycloalkyloxyiminomethylene radical, or a cycloalkylene-1,1 radical; and n = 0 to 4 provided that the radicals or phenyl or heterocyclyl portions mentioned above can optionally be substituted, in the enantiomeric or diastereoisomeric forms or mixtures thereof, and/or as the case may be in their syn or anti form or mixture thereof and their salts.

(57) Abrégé : Dérivés hétérocyclylalcoyl pipéridine de formule générale (I) pour lesquels: X_1, X_2, X_3, X_4 et X_5 sont >C-R'$_1$ à >C-R'$_5$ ou bien l'un au plus représente N, R_2 est COOH, alcoyloxycarbonyle, cycloalcoyloxycarbonyle, CN, -CONRaRb ou R_2 est CH_2OH, alcoyle substitué ou R_2 est -CF_2-Rc, -$C(CH_3)_2$-Rc, -CO-Rc, -CHOH-Rc, -C(cycloalcoyle)-Rc ou -CH=CH-Rc, R_3 est phényle, hétérocyclyle, alk-R"$_3$, Y représente >CH-Re ou un radical difluorométhylène, carbonyle, hydroxyiminométhylène, alcoyloxyiminométhylène, cycloalcoyloxyiminométhylène, ou un radical cycloalcoylène-1,1, et n = 0 à 4 étant entendu que les radicaux ou portions phényle ou hétérocyclyle mentionnés ci-dessus peuvent être éventuellement substitués, sous leurs formes énantiomères ou diastéréoisomères ou les mélanges de ces formes, et/ou le cas échéant sous leur forme syn ou anti ou leur mélange ainsi que leurs sels.

WO 02/40474 A2

Publiée :
— *sans rapport de recherche internationale, sera republiée dès réception de ce rapport*

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